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(54) Title: CNGH0004 POLYPEPTIDES, ANTIBODIES, COMPOSITIONS, METHODS AND USES

(57) Abstract: The present invention relates to at least one novel CNGH0004 polypeptides, antibodies, including isolated nucleic acids that encode at least one CNGH0004 polypeptide or antibody, CNGH0004 vectors, host cells, transgenic animals or plants, and methods of making and using thereof, including therapeutic compositions, methods and devices.

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**CNGH0004 POLYPEPTIDES, ANTIBODIES,  
COMPOSITIONS, METHODS AND USES****BACKGROUND OF THE INVENTION****FIELD OF THE INVENTION**

10 The present invention relates to at least one CNGH0004 polypeptide or fragment thereof, and antibodies and anti-idiotype antibodies specific therefore, as well as nucleic acids encoding such CNGH0004 polypeptides, fragments, antibodies, complementary nucleic acids, vectors, host cells, and methods of making and using thereof, including therapeutic formulations, administration and devices.

**15 RELATED ART**

Psoriasis is a genetic, multifactorial, chronic inflammatory skin disease, with a prevalence of 2.6% of the US population. The disease is characterized by pronounced hyperproliferation of keratinocytes, which results in rapid epidermal turnover and thickened, scaly, red plaques observed clinically. Other prominent histopathological features of the disease are alterations of cytokine production, fibroblast activation, vascular expansion, and leukocyte infiltration in the dermis and the epidermis. Dysregulation in cytokine production from both activated cells in the dermis and the immune cells seems to play an important role in mediating the inflammatory events associated with psoriasis. To this end, a number of changes in gene and/or protein expression have been described previously in psoriasis and some of these genes and/or proteins have also been found to be associated with other inflammatory diseases. These include proinflammatory cytokines such as IL-1 and TNF $\alpha$ , adhesion molecules such as intercellular adhesion molecule 1 (ICAM1) and vascular adhesion molecule 1 (VCAM1), chemokines, and defensins. Recently, gene expression microarray technology has been applied to profile gene expression patterns in normal versus psoriatic lesional skins on a more inclusive scale and has provided new insights to the pathogenesis of psoriasis.

30 cDNA microarray technology provides a format for the simultaneous measurement of the expression level of thousands of genes in a single hybridization assay. It is also amenable to an automated, high-throughput format. More importantly, microarray technology can be used to discover new genes, quantify and analyze gene expression and assign functionality to genes with unknown function. With the complete sequencing of human genome, identification and cloning of new genes is now accomplished rapidly. However, to understand whether these genes encode new proteins or to further identify function of these new proteins has not been advanced as rapidly. The impediment has become one of the main reasons for the use of high throughput cDNA microarray technology in a well-

- 5 designed experimental setting to discover novel protein-encoding genes or genes with novel function that may subsequently become potential therapeutic targets for a variety of human diseases.

Accordingly, there is a need to provide CNGH0004 polypeptides or antibodies or fragments that overcome one or more of these problems, as well as improvements over known polypeptides or antibodies or fragments thereof.

10

#### SUMMARY OF THE INVENTION

This invention discloses the discovery of a novel CNGH0004 gene and polypeptides through data analysis of the microarray gene expression profiling in psoriatic lesional skin biopsy samples obtained from infliximab (REMICADE®, an anti-TNF $\alpha$  monoclonal antibody approved to treat rheumatoid arthritis and Crohn's disease) treated versus placebo treated patients. The invention sets forth sequences coding for a gene designated CNGH0004, and presents evidence for said gene the roles of a developmental and tissue remodeling regulator and as a tumor specific marker. Said sequences include nucleic acid sequences of full-length cDNA, open reading frames (ORFs), probes (e.g. for PCR), antisense, ribozymes, and vectors containing the sequences and the polypeptides encoded by them.

Compositions and methods for the therapy and diagnosis of, as non-limiting examples, psoriasis, rheumatoid arthritis, Crohn's disease, asthma, and cancer, as well as other CNGH0004 related diseases and disorders, as described herein or as known in the art. Compositions may comprise one or more protein isoforms, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses CNGH0004 protein, or a T cell that is specific for cells expressing a polypeptide encoded by the gene. Such compositions may be used, for example, for the prevention and treatment of diseases such as psoriasis, asthma, and brain-, colon-, skin- and/or breast cancer. Diagnostic and prognostic methods based on detecting CNGH0004 protein, or mRNA encoding such a protein, in a sample are also disclosed.

The present invention provides isolated CNGH0004 polypeptides and encoding nucleic acid, as well as CNGH0004 human, primate, rodent, mammalian, chimeric, or human CNGH0004 polypeptides, antibodies, immunoglobulins, cleavage products and other specified portions and variants thereof, as well as CNGH0004 polypeptide or antibody compositions, encoding or complementary nucleic acids, vectors, host cells, compositions, formulations, devices, transgenic animals, transgenic plants, and methods of making and using thereof, as described and enabled herein, in combination with what is known in the art.

The present invention also provides at least one isolated CNGH0004 antibody as described herein. An antibody according to the present invention can include any polypeptide or peptide

- 5 containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) (also termed the hypervariable region or HV) of a heavy or light chain variable region, or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, wherein the antibody can be incorporated into an antibody of the present invention.
- 10 An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, or any combination thereof, and the like.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding specific CNGH0004 polypeptides or antibodies, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising at least one of said CNGH0004 polypeptide or antibody encoding or complementary nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such antibody nucleic acids, vectors and/or host cells.

20 At least one antibody of the invention binds at least one specified epitope specific to at least one CNGH0004 polypeptide, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of said polypeptide, which epitope is preferably comprised of at least 1-5 amino acids of at least one portion thereof, such as but not limited to, at least one functional, extracellular, soluble, hydrophilic, external or cytoplasmic domain of said polypeptide, or any portion thereof.

25 The at least one antibody can optionally comprise at least one specified portion of at least one complementarity determining region (CDR) (e.g., CDR1, CDR2 or CDR3 of the heavy or light chain variable region) and optionally at least one constant or variable framework region or any portion thereof. The at least one antibody amino acid sequence can further optionally comprise at least one specified substitution, insertion or deletion as described herein or as known in the art.

30 The present invention also provides at least one isolated CNGH0004 polypeptide or antibody as described herein, wherein the antibody has at least one activity. An CNGH0004 polypeptide antibody can thus be screened for a corresponding activity according to known methods, such as but not limited to, at least one biological activity towards a CNGH0004 polypeptide or polypeptide related function.

35 The present invention further provides at least one CNGH0004 anti-idiotype antibody to at least one CNGH0004 antibody of the present invention. The anti-idiotype antibody includes any

- 5 polypeptide or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, that can be incorporated into an antibody of the present invention. An antibody of the invention can include or be
- 10 derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, and the like. The present invention provides, in one aspect, isolated nucleic acid molecules comprising complementary, or hybridizing to, a polynucleotide encoding at least one CNGH0004 anti-idiotype antibody, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said CNGH0004 anti-idiotype antibody encoding nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such anti-idiotype antibody nucleic acids, vectors and/or host cells.
- 15

The present invention also provides at least one method for expressing at least one CNGH0004 polypeptide or antibody, or CNGH0004 anti-idiotype antibody, in a host cell, comprising culturing a host cell as described herein under conditions wherein at least one CNGH0004 antibody is expressed in detectable and/or recoverable amounts.

20 The present invention also provides at least one composition comprising (a) an isolated CNGH0004 polypeptide or antibody encoding nucleic acid and/or polypeptide or antibody as described herein; and (b) a suitable carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, such as but not limited to known carriers or diluents. The composition can optionally further comprise at least one further compound, polypeptide or composition.

25 The present invention further provides at least one CNGH0004 polypeptide or antibody method or composition, for administering a therapeutically effective amount to modulate or treat at least one CNGH0004 related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

30 The present invention also provides at least one composition, device and/or method of delivery of a therapeutically or prophylactically effective amount of at least one CNGH0004 polypeptide or antibody, according to the present invention.

35 The present invention further provides at least one CNGH0004 polypeptide or antibody method or composition, for diagnosing at least one CNGH0004 related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

5 The present invention also provides at least one composition, device and/or method of delivery for diagnosing of at least one CNGH0004 polypeptide or antibody, according to the present invention.

In another aspect, the present invention provides at least one isolated mammalian CNGH0004 polypeptide, comprising the amino acid sequences as part of SEQ ID NO:1.

Also provided is an isolated nucleic acid encoding at least one isolated mammalian CNGH0004 polypeptide; an isolated nucleic acid vector comprising the isolated nucleic acid, and/or a prokaryotic or eukaryotic host cell comprising the isolated nucleic acid. The host cell can optionally be at least one selected from prokaryotic or eukaryotic cells, or fusion cells thereof, e.g., but not limited to, mammalian, plant or insect, such as but not limited to, CHO, myeloma, or lymphoma cells, bacterial cells, yeast cells, silk worm cells, or any derivative, immortalized or transformed cell thereof. Also provided is a method for producing at least one CNGH0004 polypeptide, comprising translating the polypeptide encoding nucleic acid under conditions *in vitro*, *in vivo* or *in situ*, such that the CNGH0004 polypeptide is expressed in detectable or recoverable amounts.

Also provided is a composition comprising at least one isolated mammalian CNGH0004 polypeptide and at least one pharmaceutically acceptable carrier or diluent. The composition can optionally further comprise an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is a method for diagnosing or treating a CNGH0004 related condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one isolated mammalian CNGH0004 polypeptide of the invention with, or to, the cell, tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.0000001-500 mg/kilogram per: 1-24 hours, 1-7 days, 1-52 weeks, 1-24 months, 1-30 years (or any range or value

5 therein), of the cells, tissue, organ or animal. The method can optionally further comprise using the contacting or the administrating by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, 10 intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or protein selected from at least one of an 15 anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. The method can optionally further comprise administering, prior, concurrently or after the (a) 20 contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an antirhèumatic, a muscle relaxant, a narcotic, an anti-inflammatory, a non-steroid inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an 25 immunization, an immunoglobulin, an immunosuppressive, a hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is at least one medical device, comprising at least one isolated mammalian

CNGH0004 polypeptide of the invention, wherein the device is suitable to contacting or 30 administering the at least one CNGH0004 polypeptide by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

Also provided is an article of manufacture for human pharmaceutical or diagnostic use,

5 comprising packaging material and a container comprising a solution or a lyophilized form of at least one isolated mammalian CNGH0004 polypeptide of the present invention. The article of manufacture can optionally comprise having the container as a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, 10 intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

Also provided is a method for producing at least one isolated mammalian CNGH0004 15 polypeptide of the present invention, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts the polypeptide. Further provided in the present invention is at least one CNGH0004 polypeptide produced by the above method.

In another aspect the present invention provides at least one isolated mammalian CNGH0004 20 antibody, comprising at least one human CDR, wherein the antibody specifically binds at least one epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:1.

The at least one antibody can optionally further comprise at least one characteristic selected from: (i) bind CNGH0004 with an affinity of at least one selected from at least  $10^9$  M, at least  $10^{10}$  M, 25 at least  $10^{11}$  M, or at least  $10^{12}$  M; and/or (ii) substantially neutralizes at least one activity of at least one CNGH0004 polypeptide. Also provided is an isolated nucleic acid encoding at least one isolated mammalian CNGH0004 antibody; an isolated nucleic acid vector comprising the isolated nucleic acid, and/or a prokaryotic or eukaryotic host cell comprising the isolated nucleic acid. The host cell can 30 optionally be at least one selected from prokaryotic or eukaryotic cells, or fusion cells thereof, e.g., but not limited to, mammalian, plant or insect, such as but not limited to, CHO, myeloma, or lymphoma cells, bacterial cells, yeast cells, silk worm cells, or any derivative, immortalized or transformed cell thereof. Also provided is a method for producing at least one CNGH0004 antibody, comprising translating the antibody encoding nucleic acid under conditions in vitro, in vivo or in situ, such that the CNGH0004 antibody is expressed in detectable or recoverable amounts.

Also provided is a composition comprising at least one isolated mammalian CNGH0004 35 antibody and at least one pharmaceutically acceptable carrier or diluent. The composition can optionally further comprise an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug,

- 5 a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a  
10 neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

15 The present invention further provides an anti-idiotype antibody or fragment that specifically binds at least one isolated mammalian CNGH0004 antibody of the present invention.

Also provided is a method for diagnosing or treating a CNGH0004 related condition in a cell, tissue, organ or animal, comprising

- (a) contacting or administering a composition comprising an effective amount of at least one  
20 isolated mammalian CNGH0004 antibody of the invention with, or to, the cell, tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.0001-500 mg/kilogram of the cells, tissue, organ or animal. The method can optionally further comprise using the contacting or the administrating by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular,  
25 intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.  
30 The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. The method can optionally further comprise  
35 administering, prior, concurrently or after the (a) contacting or administering, at least one composition.

5 comprising an effective amount of at least one compound or protein selected from at least one of a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, an anti-inflammatory, a non-steroid inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a hormone, a 10 hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is at least one medical device, comprising at least one isolated mammalian CNGH0004 antibody of the invention, wherein the device is suitable to contacting or administering the at least one CNGH0004 antibody by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, 15 intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, 20 intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

Also provided is an article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising a solution or a lyophilized form of at least one isolated mammalian CNGH0004 antibody of the present invention. The article of manufacture can optionally comprise having the container as a component of a parenteral, subcutaneous, 25 intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, 30 intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

Also provided is a method for producing at least one isolated mammalian CNGH0004 antibody of the present invention, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts the antibody. Further provided in the 35 present invention is at least one CNGH0004 antibody produced by the above method.

The present invention further provides any invention described herein.

## 5

## DESCRIPTION OF THE INVENTION

The present invention provides isolated, recombinant and/or synthetic human CNGH0004 protein, as well as human, primate, rodent, mammalian, chimeric, humanized or CDR-grafted, antibodies and CNGH0004 anti-idiotype antibodies thereto, and compositions and encoding nucleic acid molecules comprising at least one polynucleotide encoding at least one CNGH0004 protein,

10 antibody or anti-idiotype antibody. The present invention further includes, but is not limited to, methods of making and using such nucleic acids and antibodies and anti-idiotype antibodies, including diagnostic and therapeutic compositions, methods and devices.

As used herein, an "CNGH0004 antibody," "CNGH0004 antibody," and the like include any 15 polypeptide or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion, fragment or variant thereof, or at least one portion of an CNGH0004 receptor or binding polypeptide, which can be incorporated into a CNGH0004 antibody of the present invention.

20 Antibodies can include one or more of at least one CDR, at least one variable region, at least one constant region, at least one heavy chain (e.g.,  $\gamma_1$ ,  $\gamma_2$ ,  $\gamma_3$ ,  $\gamma_4$ ,  $\mu$ ,  $\alpha_1$ ,  $\alpha_2$ ,  $\delta$ ,  $\epsilon$ ), at least one light chain (e.g.,  $\kappa$  and  $\lambda$ ), or any portion or fragment thereof, and can further comprise interchain and intrachain disulfide bonds, hinge regions, glycosylation sites that can be separated by a hinge region, as well as heavy chains and light chains. Light chains typically have a molecular weight of about 25Kd and

25 heavy chains typically range from 50K-77Kd. Light chains can exist in two distinct forms or isotypes, kappa ( $\kappa$ ) and lambda ( $\lambda$ ), which can combine with any of the heavy chain types. All light chains have at least one variable region and at least one constant region. The IgG antibody is considered a typical antibody structure and has two intrachain disulfide bonds in the light chain (one in variable region and one in the constant region), with four in the heavy chain, and such bond encompassing a peptide loop of about 60-70 amino acids comprising a "domain" of about 110 amino acids in the chain. IgG 30 antibodies can be characterized into four classes, IgG1, IgG2, IgG3 and IgG4. Each immunoglobulin class has a different set of functions. The following table summarizes the Physicochemical properties of each of the immunoglobulins classes and subclasses.

Property	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	SIgA	IgD	IgE
Heavy Chain	$\gamma_1$	$\gamma_1$	$\gamma_1$	$\gamma_1$	$\mu$	$\alpha_1$	$\alpha_2$	$\alpha_1 / \alpha_2$	$\delta$	$\epsilon$
Mean Serum conc. (mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.05	0.03	0.00005

Sedimentation constant	7s	7s	7s	7s	19s	7s	7s	11s	7s	8s
Mol. Wt. (X 10 <sup>3</sup> )	146	146	170	146	970	160	160	385	184	188
Half Life (days)	21	20	7	21	10	6	6	?	3	2
% intravascular distribution	45	45	45	45	80	42	42	Trace	75	50
Carbohydrate (%)	2-3	2-3	2-3	2-3	12	7-11	7-11	7-11	9-14	12

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The following table summarizes non-limiting examples of antibody effector functions for human antibody classes and subclasses.

Effector function	IgG1	IgG2	IgG3	IgG4	IgM	IgA	IgD	IgE
Complement fixation	++	+	+++	-	+++	-	-	-
Placental transfer	+	+	+	+	-	-	-	-
Binding to Staph A	+++	+++	-	+++	-	-	-	-
Binding to Strep G	+++	+++	+++	+++	-	-	-	-

Accordingly, the type of antibody or fragment thereof can be selected for use according to the present invention based on the desired characteristics and functions that are desired for a particular therapeutic or diagnostic use, such as but not limited to serum half life, intravascular distribution, complement fixation, etc.

Antibody diversity is generated by at least 5 mechanisms, including (1) the use of multiple genes encoding parts of the antibody; (2) somatic mutation, e.g., primordial V gene mutation during

15 B-cell ontogeny to produce different V genes in different B-cell clones; (3) somatic recombination, e.g., gene segments J1-Jn recombine to join the main part of the V-region gene during B-cell ontogeny; (4) gene conversion where sections of DNA from a number of pseudo V region can be copied into the V region to alter the DNA sequence; and (5) nucleotide addition, e.g., when V and J regions are cut, before joining, and extra nucleotides may be inserted to code for additional amino acids. Non-limiting examples include, but are not limited to, (i) the selection/recombination of V<sub>K</sub>, J, and C<sub>K</sub> regions from germ line to B-cell clones to generate kappa chains; (ii) selection/recombination of V<sub>λ</sub>, J, and C<sub>λ</sub> regions from germ line to B-cell clones to generate lambda chains; (iii) selection/recombination of V<sub>H</sub>, D1-D30 and J<sub>H1</sub>-J<sub>H6</sub> genes to form a functional VDJ gene encoding a heavy chain variable region.

The above mechanisms work in a coordinated fashion to generate antibody diversity and specificity.

25 The term "antibody" is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian CNGH0004. For example, antibody fragments

- 5 capable of binding to CNGH0004 or portions thereof, including, but not limited to Fab (e.g., by papain digestion), Fab' (e.g., by pepsin digestion and partial reduction) and F(ab')<sub>2</sub> (e.g., by pepsin digestion), fabc (e.g., by plasmin digestion), pFc' (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments, are encompassed by the invention (see, e.g., Colligan, et al., eds., *Current Protocols in*
- 10 *Immunology*, John Wiley & Sons, Inc., NY (1994-2001)).

Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a F(ab')<sub>2</sub> heavy chain portion can 15 be designed to include DNA sequences encoding the CH<sub>1</sub> domain and/or hinge region of the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous polypeptide using genetic engineering techniques.

As used herein, the term "human antibody" refers to an antibody in which substantially every part of the polypeptide (e.g., CDR, framework, C<sub>L</sub>, C<sub>H</sub> domains (e.g., C<sub>H</sub>1, C<sub>H</sub>2, C<sub>H</sub>3), hinge, (V<sub>L</sub>, V<sub>H</sub>)) 20 is substantially non-immunogenic in humans, with only minor sequence changes or variations. Similarly, antibodies designated primate (monkey, baboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pig, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, family specific antibodies. Further, chimeric antibodies include any combination of the above. Such changes or variations optionally and preferably retain or reduce the immunogenicity in 25 humans or other species relative to non-modified antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when a human antibody is a single chain antibody, it can comprise a linker peptide that is not found in native human antibodies. 30 For example, an Fv can comprise a linker peptide, such as two to about eight glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

Bispecific, heterospecific, heteroconjugate or similar antibodies can also be used that are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two 35 different antigens. In the present case, one of the binding specificities is for at least one CNGH0004 polypeptide, the other one is for any other antigen. Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-

5 expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed, e.g., in WO 93/08829, US Patent Nos, 6210668, 6193967, 6132992, 6106833, 6060285, 6037453, 6010902, 5989530, 5959084, 5959083, 5932448, 5833985, 5821333, 5807706, 5643759, 5601819, 5582996, 5496549, 4676980, WO 91/00360, WO 92/00373, EP 03089, Traunecker et al., EMBO J. 10:3655 (1991), Suresh et al., Methods in Enzymology 121:210 (1986), each entirely incorporated herein by reference.

10 15 Such antibodies optionally further affect a specific ligand, such as but not limited to where such antibody modulates, decreases, increases, antagonizes, agonizes, mitigates, alleviates, blocks, inhibits, abrogates and/or interferes with at least one CNGH0004 activity or binding, or with CNGH0004 receptor activity or binding, *in vitro*, *in situ* and/or *in vivo*. As a non-limiting example, a suitable CNGH0004 antibody, specified portion or variant of the present invention can bind at least one CNGH0004, or specified portions, variants or domains thereof. A suitable CNGH0004 antibody, specified portion, or variant can also optionally affect at least one of CNGH0004 activity or function, such as but not limited to, RNA, DNA or polypeptide synthesis, CNGH0004 release, CNGH0004 receptor signaling, membrane CNGH0004 cleavage, CNGH0004 activity, CNGH0004 production and/or synthesis.

20 25 30 35 CNGH0004 antibodies (also termed CNGH0004 antibodies) useful in the methods and compositions of the present invention can optionally be characterized by high affinity binding to CNGH0004 and optionally and preferably having low toxicity. In particular, an antibody, specified fragment or variant of the invention, where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably possess low immunogenicity, is useful in the present invention. The antibodies that can be used in the invention are optionally characterized by their ability to treat patients for extended periods with measurable alleviation of symptoms and low and/or acceptable toxicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAHA, HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably less than about 100 measured with a double

5 antigen enzyme immunoassay) (Elliott *et al.*, *Lancet* 344:1125-1127 (1994), entirely incorporated herein by reference).

#### Utility

CNGH0004 protein is predicted to be an extracellular matrix protein. All CNGH0004 protein domains are characterized as extracellular domains. In addition to normal placenta and fetal tissue development, protein domains that constitute CNGH0004 are probably also involved in tissue remodeling of airway smooth muscle as well as psoriatic epithelium. Based on its domain structure, CNGH0004 may function through mediating adhesion via metal ion-dependent adhesion sites (MIDAS), or via modulating complement control related to immunological responses. As such, CNGH0004 is a potential therapeutic target for treatment of autoimmune or chronic inflammatory diseases including, but not limited to psoriasis or asthma, and different types of cancers.

The isolated nucleic acids of the present invention can be used for production of at least one CNGH0004 antibody or specified variant thereof, which can be used to measure or effect in a cell, tissue, organ or animal (including mammals and humans), to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one CNGH0004 condition, selected from, but not limited to, at least one of an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease, or other known or specified CNGH0004 related condition.

Such a method can comprise administering an effective amount of a composition or a pharmaceutical composition comprising at least one CNGH0004 antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment, alleviation, prevention, or reduction in symptoms, effects or mechanisms. The effective amount can comprise an amount of about 0.001 to 500 mg/kg per single (e.g., bolus), multiple or continuous administration, or to achieve a serum concentration of 0.01-5000 µg/ml serum concentration per single, multiple, or continuous administration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

#### Citations

All publications or patents cited herein are entirely incorporated herein by reference as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats. The following references are entirely incorporated herein by reference: Ausubel, *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, *et al.*, *Molecular Cloning: A Laboratory Manual*, 2<sup>nd</sup> Edition, Cold Spring Harbor, NY (1989); Harlow and

- 5 Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Polypeptide Science, John Wiley & Sons, NY, NY, (1997-2001).

Antibodies of the Present Invention.

- At least one CNGH0004 antibody of the present invention can be optionally produced by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells, as well known in the art. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Polypeptide Science, John Wiley & Sons, NY, NY, (1997-2001), each entirely incorporated herein by reference.

Human antibodies that are specific for human CNGH0004 polypeptides or fragments thereof can be raised against an appropriate immunogenic antigen, such as isolated and/or CNGH0004 polypeptide or a portion thereof (including synthetic molecules, such as synthetic peptides). Other specific or general mammalian antibodies can be similarly raised. Preparation of immunogenic antigens, and monoclonal antibody production can be performed using any suitable technique.

In one approach, a hybridoma is produced by fusing a suitable immortal cell line (e.g., a myeloma cell line such as, but not limited to, Sp2/0, Sp2/0-AG14, NSO, NS1, NS2, AE-1, L5, >243, P3X63Ag8.653, Sp2 SA3, Sp2 MA1, Sp2 SS1, Sp2 SA5, U937, MLA 144, ACT IV, MOLT4, DA-1, 25 JURKAT, WEHI, K-562, COS, RAJI, NIH 3T3, HL-60, MLA 144, NAMAIWA, NEURO 2A, or the like, or heteromyomas, fusion products thereof, or any cell or fusion cell derived therefrom, or any other suitable cell line as known in the art. See, e.g., www.atcc.org, www.lifetech.com, and the like, with antibody producing cells, such as, but not limited to, isolated or cloned spleen, peripheral blood, lymph, tonsil, or other immune or B cell containing cells, or any other cells expressing heavy or light 30 chain constant or variable or framework or CDR sequences, either as endogenous or heterologous nucleic acid, as recombinant or endogenous, viral, bacterial, algal, prokaryotic, amphibian, insect, reptilian, fish, mammalian, rodent, equine, ovine, goat, sheep, primate, eukaryotic, genomic DNA, cDNA, rDNA, mitochondrial DNA or RNA, chloroplast DNA or RNA, hnRNA, mRNA, tRNA, single, double or triple stranded, hybridized, and the like or any combination thereof. See, e.g., Ausubel, 35 supra, and Colligan, Immunology, supra, chapter 2, entirely incorporated herein by reference.

Antibody producing cells can also be obtained from the peripheral blood or, preferably the spleen or lymph nodes, of humans or other suitable animals that have been immunized with the antigen of interest. Any other suitable host cell can also be used for expressing heterologous or endogenous

- 5 nucleic acid encoding an antibody, specified fragment or variant thereof, of the present invention. The fused cells (hybridomas) or recombinant cells can be isolated using selective culture conditions or other suitable known methods, and cloned by limiting dilution or cell sorting, or other known methods. Cells which produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).
- 10 Other suitable methods of producing or isolating antibodies of the requisite specificity can be used, including, but not limited to, methods that select recombinant antibody from a peptide or polypeptide library (e.g., but not limited to, a bacteriophage, ribosome, oligonucleotide, RNA, cDNA, or the like, display library; e.g., as available from Cambridge antibody Technologies, Cambridgeshire, UK; MorphoSys, Martinsreid/Planegg, DE; Biovation, Aberdeen, Scotland, UK; BioInvent, Lund, Sweden; Dyax Corp., Enzon, Affymax/Biosite; Xoma, Berkeley, CA; Ixsys. See, e.g., EP 368,684, PCT/GB91/01134; PCT/GB92/01755; PCT/GB92/002240; PCT/GB92/00883; PCT/GB93/00605; US 08/350260(5/12/94); PCT/GB94/01422; PCT/GB94/02662; PCT/GB97/01835; (CAT/MRC); WO90/14443; WO90/14424; WO90/14430; PCT/US94/1234; WO92/18619; WO96/07754; (Scripps); EP 614 989 (MorphoSys); WO95/16027 (BioInvent); WO88/06630; WO90/3809 (Dyax); US 4,704,692 (Enzon); PCT/US91/02989 (Affymax); WO89/06283; EP 371 998; EP 550 400; (Xoma); EP 229 046; PCT/US91/07149 (Ixsys); or stochastically generated peptides or polypeptides - US 5723323, 5763192, 5814476, 5817483, 5824514, 5976862, WO 86/05803, EP 590 689 (Ixsys, now Applied Molecular Evolution (AME), each entirely incorporated herein by reference) or that rely upon immunization of transgenic animals (e.g., SCID mice, Nguyen et al., *Microbiol. Immunol.* 41:901-907 (1997); Sandhu et al., *Crit. Rev. Biotechnol.* 16:95-118 (1996); Eren et al., *Immunol.* 93:154-161 (1998), each entirely incorporated by reference as well as related patents and applications) that are capable of producing a repertoire of human antibodies, as known in the art and/or as described herein. Such techniques, include, but are not limited to, ribosome display (Hanes et al., *Proc. Natl. Acad. Sci. USA*, 94:4937-4942 (May 1997); Hanes et al., *Proc. Natl. Acad. Sci. USA*, 95:14130-14135 (Nov. 1998)); single cell antibody producing technologies (e.g., selected lymphocyte antibody method ("SLAM") (US pat. No. 5,627,052, Wen et al., *J. Immunol.* 17:887-892 (1987); Babcock et al., *Proc. Natl. Acad. Sci. USA* 93:7843-7848 (1996)); gel microdroplet and flow cytometry (Powell et al., *Biotechnol.* 8:333-337 (1990); One Cell Systems, Cambridge, MA; Gray et al., *J. Imm. Meth.* 182:155-163 (1995); Kenny et al., *Bio/Technol.* 13:787-790 (1995)); B-cell selection (Steenbakkers et al., *Molec. Biol. Reports* 19:125-134 (1994); Jonak et al., *Progress Biotech*, Vol. 5, In Vitro Immunization in Hybridoma Technology, Borrebaeck, ed., Elsevier Science Publishers B.V., Amsterdam, Netherlands (1988)).

5       Methods for engineering or humanizing non-human or human antibodies can also be used and  
are well known in the art. Generally, a humanized or engineered antibody has one or more amino acid  
residues from a source which is non-human, e.g., but not limited to mouse, rat, rabbit, non-human  
primate or other mammal. These human amino acid residues are often referred to as "import" residues,  
which are typically taken from an "import" variable, constant or other domain of a known human  
10 sequence. Known human Ig sequences are disclosed, e.g., [www.ncbi.nlm.nih.gov/entrez/query.fcgi](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi);  
[www.atcc.org/phage/hdb.html](http://www.atcc.org/phage/hdb.html); [www.sciquest.com/](http://www.sciquest.com/); [www.abcam.com/](http://www.abcam.com/);  
[www.antibodyresource.com/onlinecomp.html](http://www.antibodyresource.com/onlinecomp.html); [www.public.iastate.edu/~pedro/research\\_tools.html](http://www.public.iastate.edu/~pedro/research_tools.html);  
[www.mgen.uni-heidelberg.de/SD/IT/IT.html](http://www.mgen.uni-heidelberg.de/SD/IT/IT.html); [www.whfreeman.com/immunology/CH05/kuby05.htm](http://www.whfreeman.com/immunology/CH05/kuby05.htm);  
[www.library.thinkquest.org/12429/Immune/Antibody.html](http://www.library.thinkquest.org/12429/Immune/Antibody.html); [www.hhmi.org/grants/lectures/1996/vlab/](http://www.hhmi.org/grants/lectures/1996/vlab/);  
15      [www.path.cam.ac.uk/~mrc7/mikeimages.html](http://www.path.cam.ac.uk/~mrc7/mikeimages.html); [www.antibodyresource.com/](http://www.antibodyresource.com/);  
[mcb.harvard.edu/BioLinks/Immunology.html](http://mcb.harvard.edu/BioLinks/Immunology.html); [www.immunologylink.com/](http://www.immunologylink.com/);  
[pathbox.wustl.edu/~hcenter/index.html](http://pathbox.wustl.edu/~hcenter/index.html); [www.biotech.usf.edu/~hcl/](http://www.biotech.usf.edu/~hcl/);  
[www.pebio.com/pa/340913/340913.html](http://www.pebio.com/pa/340913/340913.html); [www.nal.usda.gov/awic/pubs/antibody/](http://www.nal.usda.gov/awic/pubs/antibody/);  
[www.m.ehime-u.ac.jp/~yasuhito/Elisa.html](http://www.m.ehime-u.ac.jp/~yasuhito/Elisa.html); [www.biodesign.com/table.asp](http://www.biodesign.com/table.asp);  
20      [www.icnet.uk/axp/facs/davies/links.html](http://www.icnet.uk/axp/facs/davies/links.html); [www.biotech.usf.edu/~fccl/protocol.html](http://www.biotech.usf.edu/~fccl/protocol.html); [www.isac-net.org/sites\\_geo.html](http://www.isac-net.org/sites_geo.html); [aximt1.jmt.uni-marburg.de/~rek/AEPStart.html](http://aximt1.jmt.uni-marburg.de/~rek/AEPStart.html);  
[baserv.uci.kun.nl/~jraats/links1.html](http://baserv.uci.kun.nl/~jraats/links1.html); [www.recab.uni-hd.de/immuno.bme.nwu.edu/](http://www.recab.uni-hd.de/immuno.bme.nwu.edu/); [www.mrc-cpe.cam.ac.uk/jmt-doc/public/INTRO.html](http://www.mrc-cpe.cam.ac.uk/jmt-doc/public/INTRO.html); [www.ibt.unam.mx/vir/V\\_mice.html](http://www.ibt.unam.mx/vir/V_mice.html); [imgt.cnusc.fr:8104/](http://imgt.cnusc.fr:8104/);  
[www.biochem.ucl.ac.uk/~martin/abs/index.html](http://www.biochem.ucl.ac.uk/~martin/abs/index.html); [antibody.bath.ac.uk/](http://antibody.bath.ac.uk/);  
25      [abgen.cvm.tamu.edu/lab/wwwabgen.html](http://abgen.cvm.tamu.edu/lab/wwwabgen.html); [www.unizh.ch/~honegger/AHOseminar/Slide01.html](http://www.unizh.ch/~honegger/AHOseminar/Slide01.html);  
[www.cryst.bbk.ac.uk/~ubcg07s/](http://www.cryst.bbk.ac.uk/~ubcg07s/); [www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm](http://www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm);  
[www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html](http://www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html);  
[www.ibt.unam.mx/vir/structure/stat\\_aim.html](http://www.ibt.unam.mx/vir/structure/stat_aim.html); [www.biosci.missouri.edu/smithgp/index.html](http://www.biosci.missouri.edu/smithgp/index.html);  
[www.cryst.bioc.cam.ac.uk/~fmolina/Web-pages/Pept/spottech.html](http://www.cryst.bioc.cam.ac.uk/~fmolina/Web-pages/Pept/spottech.html); [www.jerini.de/fr\\_products.htm](http://www.jerini.de/fr_products.htm);  
30      [www.patents.ibm.com/ibm.html](http://www.patents.ibm.com/ibm.html). Kabat et al., Sequences of Polypeptides of Immunological Interest,  
U.S. Dept. Health (1983), each entirely incorporated herein by reference.

Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art. Generally part or all of the non-human or human CDR sequences are maintained while the non-human sequences of the variable and constant regions are replaced with human or other amino acids. Antibodies can also optionally be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, humanized antibodies can be

- 5     optionally prepared by a process of analysis of the parental sequences and various conceptual  
humanized products using three-dimensional models of the parental and humanized sequences. Three-  
dimensional immunoglobulin models are commonly available and are familiar to those skilled in the  
art. Computer programs are available which illustrate and display probable three-dimensional  
conformational structures of selected candidate immunoglobulin sequences. Inspection of these  
10    displays permits analysis of the likely role of the residues in the functioning of the candidate  
immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate  
immunoglobulin to bind its antigen. In this way, framework residues can be selected and combined  
from the consensus and import sequences so that the desired antibody characteristic, such as increased  
affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most  
15    substantially involved in influencing antigen binding. Humanization or engineering of antibodies of  
the present invention can be performed using any known method, such as but not limited to those  
described in, Winter (Jones et al., *Nature* 321:522 (1986); Riechmann et al., *Nature* 332:323 (1988);  
Verhoeyen et al., *Science* 239:1534 (1988)), Sims et al., *J. Immunol.* 151: 2296 (1993); Chothia and  
Lesk, *J. Mol. Biol.* 196:901 (1987), Carter et al., *Proc. Natl. Acad. Sci. U.S.A.* 89:4285 (1992); Presta  
20    et al., *J. Immunol.* 151:2623 (1993), US patent Nos: 5723323, 5976862, 5824514, 5817483, 5814476,  
5763192, 5723323, 5,766886, 5714352, 6204023, 6180370, 5693762, 5530101, 5585089, 5225539;  
4816567, PCT/ US98/16280, US96/18978, US91/09630; US91/05939, US94/01234, GB89/01334,  
GB91/01134, GB92/01755; WO90/14443, WO90/14424, WO90/14430, EP 229246, each entirely  
incorporated herein by reference, included references cited therein.  
25    The CNGH0004 antibody can also be optionally generated by immunization of a transgenic  
animal (e.g., mouse, rat, hamster, non-human primate, and the like) capable of producing a repertoire  
of human antibodies, as described herein and/or as known in the art. Cells that produce a human  
CNGH0004 antibody can be isolated from such animals and immortalized using suitable methods, such  
as the methods described herein and/or as known in the art.  
30    Transgenic mice that can produce a repertoire of human antibodies that bind to human antigens  
can be produced by known methods (e.g., but not limited to, U.S. Pat. Nos: 5,770,428, 5,569,825,  
5,545,806, 5,625,126, 5,625,825, 5,633,425, 5,661,016 and 5,789,650 issued to Lonberg et al.;  
Jakobovits et al. WO 98/50433, Jakobovits et al. WO 98/24893, Lonberg et al. WO 98/24884, Lonberg  
et al. WO 97/13852, Lonberg et al. WO 94/25585, Kucherlapate et al. WO 96/34096, Kucherlapate et  
35    al. EP 0463 151 B1, Kucherlapate et al. EP 0710 719 A1, Surani et al. US. Pat. No. 5,545,807,  
Bruggemann et al. WO 90/04036, Bruggemann et al. EP 0438 474 B1, Lonberg et al. EP 0814 259 A2,  
Lonberg et al. GB 2 272 440 A, Lonberg et al. *Nature* 368:856-859 (1994), Taylor et al., *Int. Immunol.*

5 6(4)579-591 (1994), Green *et al.*, *Nature Genetics* 7:13-21 (1994), Mendez *et al.*, *Nature Genetics* 15:146-156 (1997), Taylor *et al.*, *Nucleic Acids Research* 20(23):6287-6295 (1992), Tuailon *et al.*, *Proc Natl Acad Sci USA* 90(8)3720-3724 (1993), Lonberg *et al.*, *Int Rev Immunol* 13(1):65-93 (1995) and Fishwald *et al.*, *Nat Biotechnol* 14(7):845-851 (1996), which are each entirely incorporated herein by reference). Generally, these mice comprise at least one transgene comprising DNA from at least 10 one human immunoglobulin locus that is functionally rearranged, or which can undergo functional rearrangement. The endogenous immunoglobulin loci in such mice can be disrupted or deleted to eliminate the capacity of the animal to produce antibodies encoded by endogenous genes.

Screening antibodies for specific binding to similar polypeptides or fragments can be conveniently achieved using peptide display libraries. This method involves the screening of large 15 collections of peptides for individual members having the desired function or structure. antibody screening of peptide display libraries is well known in the art. The displayed peptide sequences can be from 3 to 5000 or more amino acids in length, frequently from 5-100 amino acids long, and often from about 8 to 25 amino acids long. In addition to direct chemical synthetic methods for generating peptide 20 libraries, several recombinant DNA methods have been described. One type involves the display of a peptide sequence on the surface of a bacteriophage or cell. Each bacteriophage or cell contains the nucleotide sequence encoding the particular displayed peptide sequence. Such methods are described in PCT Patent Publication Nos. 91/17271, 91/18980, 91/19818, and 93/08278. Other systems for generating 25 libraries of peptides have aspects of both in vitro chemical synthesis and recombinant methods. See, PCT Patent Publication Nos. 92/05258, 92/14843, and 96/19256. See also, U.S. Patent Nos. 5,658,754; and 5,643,768. Peptide display libraries, vector, and screening kits are commercially available from such suppliers as Invitrogen (Carlsbad, CA), and Cambridge antibody Technologies (Cambridgeshire, UK). See, e.g., U.S. Pat. Nos. 4704692, 4939666, 4946778, 5260203, 5455030, 5518889, 5534621, 5656730, 5763733, 5767260, 5856456, assigned to Enzon; 5223409, 5403484, 5571698, 5837500, assigned to 30 Dyax, 5427908, 5580717, assigned to Affymax; 5885793, assigned to Cambridge antibody Technologies; 5750373, assigned to Genentech, 5618920, 5595898, 5576195, 5698435, 5693493, 5698417, assigned to Xoma, Colligan, *supra*; Ausubel, *supra*; or Sambrook, *supra*, each of the above patents and publications entirely incorporated herein by reference.

Antibodies of the present invention can also be prepared using at least one CNGH0004 antibody encoding nucleic acid to provide transgenic animals or mammals, such as goats, cows, horses, 35 sheep, and the like, that produce such antibodies in their milk. Such animals can be provided using known methods. See, e.g., but not limited to, US patent nos. 5,827,690; 5,849,992; 4,873,316;

- 5 5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is entirely incorporated herein by reference.

Antibodies of the present invention can additionally be prepared using at least one CNGH0004 antibody encoding nucleic acid to provide transgenic plants and cultured plant cells (e.g., but not limited to tobacco and maize) that produce such antibodies, specified portions or variants in the plant parts or in cells cultured therefrom. As a non-limiting example, transgenic tobacco leaves expressing recombinant polypeptides have been successfully used to provide large amounts of recombinant polypeptides, e.g., using an inducible promoter. See, e.g., Cramer et al., *Curr. Top. Microbiol. Immunol.* 240:95-118 (1999) and references cited therein. Also, transgenic maize have been used to express mammalian polypeptides at commercial production levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, e.g., Hood et al., *Adv. Exp. Med. Biol.* 464:127-147 (1999) and references cited therein. Antibodies have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as single chain antibodies (scFv's), including tobacco seeds and potato tubers. See, e.g., Conrad et al., *Plant Mol. Biol.* 38:101-109 (1998) and reference cited therein. Thus, antibodies of the present invention can also be produced using transgenic plants, according to known methods. See also, e.g., Fischer et al., *Biotechnol. Appl. Biochem.* 30:99-108 (Oct., 1999); Ma et al., *Trends Biotechnol.* 13:522-7 (1995); Ma et al., *Plant Physiol.* 109:341-6 (1995); Whitelam et al., *Biochem. Soc. Trans.* 22:940-944 (1994); and references cited therein. Each of the above references is entirely incorporated herein by reference.

The antibodies of the invention can bind human CNGH0004 with a wide range of affinities (K<sub>D</sub>). In a preferred embodiment, at least one human mAb of the present invention can optionally bind human CNGH0004 with high affinity. For example, a human mAb can bind human CNGH0004 with a K<sub>D</sub> equal to or less than about 10<sup>-7</sup> M, such as but not limited to, 0.1-9.9 (or any range or value therein) X 10<sup>-7</sup>, 10<sup>-8</sup>, 10<sup>-9</sup>, 10<sup>-10</sup>, 10<sup>-11</sup>, 10<sup>-12</sup>, 10<sup>-13</sup> or any range or value therein.

The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method. (See, for example, Berzofsky, et al., "Antibody-Antigen Interactions," In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis *Immunology*, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular antibody-antigen interaction can vary if measured under different conditions (e.g., salt concentration, pH). Thus, measurements of affinity and other antigen-binding parameters (e.g., K<sub>D</sub>, K<sub>a</sub>, K<sub>d</sub>) are preferably made with standardized solutions of antibody and antigen, and a standardized buffer, such as the buffer described herein.

#### Nucleic Acid Molecules

5 Using the information provided herein, such as the nucleotide sequences encoding at least 70-100% of the contiguous amino acids of at least one of SEQ ID NO:1, specified fragments, variants or consensus sequences thereof, or a deposited vector comprising at least one of these sequences, a nucleic acid molecule of the present invention encoding at least one CNGH0004 antibody can be obtained using methods described herein or as known in the art, such as but not limited to SEQ ID

10 NO:2.

Nucleic acid molecules of the present invention can be in the form of RNA, such as mRNA, hnRNA, tRNA or any other form, or in the form of DNA, including, but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combinations thereof. The DNA can be triple-stranded; double-stranded or single-stranded, or any combination thereof. Any portion of 15 at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the non-coding strand, also referred to as the anti-sense strand.

Isolated nucleic acid molecules of the present invention can include nucleic acid molecules comprising an open reading frame (ORF), optionally with one or more introns, e.g., but not limited to, at least one specified portion of at least one CDR, as CDR1, CDR2 and/or CDR3 of at least one heavy 20 chain or light chain; nucleic acid molecules comprising the coding sequence for an CNGH0004 antibody or variable region; and nucleic acid molecules which comprise a nucleotide sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode at least one CNGH0004 antibody as described herein and/or as known in the art. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to 25 generate such degenerate nucleic acid variants that code for specific CNGH0004 antibodies of the present invention. See, e.g., Ausubel, et al., *supra*, and such nucleic acid variants are included in the present invention. Non-limiting examples of isolated nucleic acid molecules of the present invention include the CDR sequences corresponding to non-limiting examples of a nucleic acid encoding, respectively, HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, LC CDR3, HC variable region 30 and LC variable region.

As indicated herein, nucleic acid molecules of the present invention which comprise a nucleic acid encoding a CNGH0004 antibody can include, but are not limited to, those encoding the amino acid sequence of an antibody fragment, by itself; the coding sequence for the entire antibody or a portion thereof; the coding sequence for an antibody, fragment or portion, as well as additional sequences, such 35 as the coding sequence of at least one signal leader or fusion peptide, intron, non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals (for example - ribosome binding and

5 stability of mRNA); an additional coding sequence that codes for additional amino acids, such as those that provide additional functionalities. Thus, the sequence encoding an antibody can be fused to a marker sequence, such as a sequence encoding a peptide that facilitates purification of the fused antibody comprising an antibody fragment or portion.

#### Polynucleotides Which Selectively Hybridize to a Polynucleotide as Described Herein

10

The present invention provides isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides. For example, polynucleotides of the present invention can be used to identify, isolate, or amplify partial or 15 full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated, or otherwise complementary to, a cDNA from a human or mammalian nucleic acid library.

20

Preferably, the cDNA library comprises at least 80% full-length sequences, preferably at least 85% or 90% full-length sequences, and more preferably at least 95% full-length sequences. The cDNA libraries can be normalized to increase the representation of rare sequences. Low or moderate stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative to complementary sequences. Moderate and high stringency conditions can optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 70% sequence identity and can be employed to identify 25 orthologous or paralogous sequences.

30

Optionally, polynucleotides of this invention will encode at least a portion of an antibody encoded by the polynucleotides described herein. The polynucleotides of this invention embrace nucleic acid sequences that can be employed for selective hybridization to a polynucleotide encoding an antibody of the present invention. See, e.g., Ausubel, *supra*; Colligan, *supra*, each entirely incorporated herein by reference.

#### Construction of Nucleic Acids

The isolated nucleic acids of the present invention can be made using (a) recombinant methods, (b) synthetic techniques, (c) purification techniques, or combinations thereof, as well-known in the art.

35

The nucleic acids can conveniently comprise sequences in addition to a polynucleotide of the present invention. For example, a multi-cloning site comprising one or more endonuclease restriction sites can be inserted into the nucleic acid to aid in isolation of the polynucleotide. Also, translatable sequences can be inserted to aid in the isolation of the translated polynucleotide of the present invention. For example, a hexa-histidine marker sequence provides a convenient means to purify the polypeptides of

5 the present invention. The nucleic acid of the present invention - excluding the coding sequence - is optionally a vector, adapter, or linker for cloning and/or expression of a polynucleotide of the present invention.

10 Additional sequences can be added to such cloning and/or expression sequences to optimize their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the introduction of the polynucleotide into a cell. Use of cloning vectors, expression vectors, adapters, and linkers is well known in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*).

#### 15 Recombinant Methods for Constructing Nucleic Acids

The isolated nucleic acid compositions of this invention, such as RNA, cDNA, genomic DNA, or any combination thereof, can be obtained from biological sources using any number of cloning methodologies known to those of skill in the art. In some embodiments, oligonucleotide probes that selectively hybridize, under stringent conditions, to the polynucleotides of the present invention are used to identify the desired sequence in a cDNA or genomic DNA library. The isolation of RNA, and construction of cDNA and genomic libraries, is well known to those of ordinary skill in the art. (See, e.g., Ausubel, *supra*, or Sambrook, *supra*)

#### 20 Nucleic Acid Screening and Isolation Methods

A cDNA or genomic library can be screened using a probe based upon the sequence of a polynucleotide of the present invention, such as those disclosed herein. Probes can be used to hybridize with genomic DNA or cDNA sequences to isolate homologous genes in the same or different organisms. Those of skill in the art will appreciate that various degrees of stringency of hybridization can be employed in the assay; and either the hybridization or the wash medium can be stringent. As the conditions for hybridization become more stringent, there must be a greater degree of complementarity between the probe and the target for duplex formation to occur. The degree of stringency can be controlled by one or more of temperature, ionic strength, pH and the presence of a partially denaturing solvent such as formamide. For example, the stringency of hybridization is conveniently varied by changing the polarity of the reactant solution through, for example, manipulation of the concentration of formamide within the range of 0% to 50%. The degree of complementarity (sequence identity) required for detectable binding will vary in accordance with the stringency of the hybridization medium and/or wash medium. The degree of complementarity will optimally be 100%, or 70-100%, or any range or value therein. However, it should be understood that minor sequence variations in the probes and primers can be compensated for by reducing the stringency of the hybridization and/or wash medium.

5 Methods of amplification of RNA or DNA are well known in the art and can be used according to the present invention without undue experimentation, based on the teaching and guidance presented herein.

Known methods of DNA or RNA amplification include, but are not limited to, polymerase chain reaction (PCR) and related amplification processes (see, e.g., U.S. Patent Nos. 4,683,195, 10 4,683,202, 4,800,159, 4,965,188, to Mullis, et al.; 4,795,699 and 4,921,794 to Tabor, et al; 5,142,033 to Innis; 5,122,464 to Wilson, et al.; 5,091,310 to Innis; 5,066,584 to Gyllensten, et al; 4,889,818 to Gelfand, et al; 4,994,370 to Silver, et al; 4,766,067 to Biswas; 4,656,134 to Ringold) and RNA mediated amplification that uses anti-sense RNA to the target sequence as a template for double-stranded DNA synthesis (U.S. Patent No. 5,130,238 to Malek, et al, with the tradename NASBA), the 15 entire contents of which references are incorporated herein by reference. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*.)

For instance, polymerase chain reaction (PCR) technology can be used to amplify the sequences of polynucleotides of the present invention and related genes directly from genomic DNA or cDNA libraries. PCR and other in vitro amplification methods can also be useful, for example, to clone nucleic acid sequences that code for polypeptides to be expressed, to make nucleic acids to use as probes for detecting the presence of the desired mRNA in samples, for nucleic acid sequencing, or for other purposes. Examples of techniques sufficient to direct persons of skill through in vitro amplification methods are found in Berger, *supra*, Sambrook, *supra*, and Ausubel, *supra*, as well as Mullis, et al., U.S. Patent No. 4,683,202 (1987); and Innis, et al., PCR Protocols A Guide to Methods and Applications, Eds., 20 Academic Press Inc., San Diego, CA (1990). Commercially available kits for genomic PCR amplification are known in the art. See, e.g., Advantage-GC Genomic PCR Kit (Clontech). Additionally, e.g., the T4 gene 32 polypeptide (Boehringer Mannheim) can be used to improve yield of long PCR products.

#### Synthetic Methods for Constructing Nucleic Acids

The isolated nucleic acids of the present invention can also be prepared by direct chemical synthesis by known methods (see, e.g., Ausubel, et al., *supra*). Chemical synthesis generally produces a single-stranded oligonucleotide, which can be converted into double-stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. One of skill in the art will recognize that while chemical synthesis of DNA can be limited to sequences of about 100 or more bases, longer sequences can be obtained by the ligation of shorter 35 sequences.

#### Recombinant Expression Cassettes

5       The present invention further provides recombinant expression cassettes comprising a nucleic acid of the present invention. A nucleic acid sequence of the present invention, for example a cDNA or a genomic sequence encoding an antibody of the present invention, can be used to construct a recombinant expression cassette that can be introduced into at least one desired host cell. A recombinant expression cassette will typically comprise a polynucleotide of the present invention operably linked to  
10 transcriptional initiation regulatory sequences that will direct the transcription of the polynucleotide in the intended host cell. Both heterologous and non-heterologous (i.e., endogenous) promoters can be employed to direct expression of the nucleic acids of the present invention.

In some embodiments, isolated nucleic acids that serve as promoter, enhancer, or other elements can be introduced in the appropriate position (upstream, downstream or in intron) of a non-heterologous  
15 form of a polynucleotide of the present invention so as to up or down regulate expression of a polynucleotide of the present invention. For example, endogenous promoters can be altered *in vivo* or *in vitro* by mutation, deletion and/or substitution.

#### Vectors And Host Cells

The present invention also relates to vectors that include isolated nucleic acid molecules of the  
20 present invention, host cells that are genetically engineered with the recombinant vectors, and the production of at least one CNGH0004 antibody by recombinant techniques, as is well known in the art. See, e.g., Sambrook, et al., *supra*; Ausubel, et al., *supra*, each entirely incorporated herein by reference.

The polynucleotides can optionally be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it can be packaged  
25 *in vitro* using an appropriate packaging cell line and then transduced into host cells.

The DNA insert should be operatively linked to an appropriate promoter. The expression constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will preferably include a translation initiating at the beginning and a termination codon (e.g., UAA, UGA or UAG) appropriately positioned at the end of the mRNA to be translated, with UAA and UAG preferred for mammalian or eukaryotic cell expression.

Expression vectors will preferably but optionally include at least one selectable marker. Such markers include, e.g., but not limited to, methotrexate (MTX), dihydrofolate reductase (DHFR, US Pat.Nos. 4,399,216; 4,634,665; 4,656,134; 4,956,288; 5,149,636; 5,179,017, ampicillin, neomycin (G418), mycophenolic acid, or glutamine synthetase (GS, US Pat.Nos. 5,122,464; 5,770,359;

- 5 5,827,739) resistance for eukaryotic cell culture, and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria or prokaryotics (the above patents are entirely incorporated hereby by reference). Appropriate culture mediums and conditions for the above-described host cells are known in the art. Suitable vectors will be readily apparent to the skilled artisan. Introduction of a vector construct into a host cell can be effected by calcium phosphate transfection, DEAE-dextran  
10 mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other known methods. Such methods are described in the art, such as Sambrook, *supra*, Chapters 1-4 and 16-18; Ausubel, *supra*, Chapters 1, 9, 13, 15, 16.

At least one antibody of the present invention can be expressed in a modified form, such as a fusion polypeptide, and can include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of an antibody to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties can be added to an antibody of the present invention to facilitate purification. Such regions can be removed prior to final preparation of an antibody or at least one fragment thereof. Such methods are described in many standard laboratory manuals, such as Sambrook, *supra*, Chapters 17.29-17.42 and 18.1-18.74; Ausubel, *supra*, Chapters 16, 17 and 18.

Those of ordinary skill in the art are knowledgeable in the numerous expression systems available for expression of a nucleic acid encoding a polypeptide of the present invention.

Alternatively, nucleic acids of the present invention can be expressed in a host cell by turning on (by manipulation) in a host cell that contains endogenous DNA encoding an antibody of the present invention. Such methods are well known in the art, e.g., as described in US patent Nos. 5,580,734, 5,641,670, 5,733,746, and 5,733,761, entirely incorporated herein by reference.

Illustrative of cell cultures useful for the production of the antibodies, specified portions or variants thereof, are mammalian cells. Mammalian cell systems often will be in the form of monolayers of cells although mammalian cell suspensions or bioreactors can also be used. A number of suitable host cell lines capable of expressing intact glycosylated polypeptides have been developed in the art, and include the COS-1 (e.g., ATCC CRL 1650), COS-7 (e.g., ATCC CRL-1651), HEK293, BHK21 (e.g., ATCC CRL-10), CHO (e.g., ATCC CRL 1610) and BSC-1 (e.g., ATCC CRL-26) cell lines, Cos-7 cells, CHO cells, hep G2 cells, P3X63Ag8.653, SP2/0-Ag14, 293 cells, HeLa cells and the like, which are readily available from, for example, American Type Culture Collection, Manassas, Va ([www.atcc.org](http://www.atcc.org)).

Preferred host cells include cells of lymphoid origin such as myeloma and lymphoma cells.

Particularly preferred host cells are P3X63Ag8.653 cells (ATCC Accession Number CRL-1580) and

- 5 SP2/0-Ag14 cells (ATCC Accession Number CRL-1851). In a particularly preferred embodiment, the recombinant cell is a P3X63Ab8.653 or a SP2/0-Ag14 cell.

Expression vectors for these cells can include one or more of the following expression control sequences, such as, but not limited to an origin of replication; a promoter (e.g., late or early SV40 promoters, the CMV promoter (US Pat.Nos. 5,168,062; 5,385,839); an HSV tk promoter, a pgk 10 (phosphoglycerate kinase) promoter, an EF-1 alpha promoter (US Pat.No. 5,266,491), at least one human immunoglobulin promoter; an enhancer, and/or processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites (e.g., an SV40 large T Ag poly A addition site), and transcriptional terminator sequences. See, e.g., Ausubel et al., *supra*; Sambrook, et al., *supra*. Other cells useful for production of nucleic acids or polypeptides of the present invention are known and/or available, 15 for instance, from the American Type Culture Collection Catalogue of Cell Lines and Hybridomas ([www.atcc.org](http://www.atcc.org)) or other known or commercial sources.

When eukaryotic host cells are employed, polyadenylation or transcription terminator sequences are typically incorporated into the vector. An example of a terminator sequence is the polyadenylation sequence from the bovine growth hormone gene. Sequences for accurate splicing of the transcript can 20 also be included. An example of a splicing sequence is the VPI intron from SV40 (Sprague, et al., J. Virol. 45:773-781 (1983)). Additionally, gene sequences to control replication in the host cell can be incorporated into the vector, as known in the art.

#### Purification of a CNGH0004 Polypeptide or Antibody

A CNGH0004 polypeptide or antibody can be recovered and purified from recombinant cell 25 cultures by well-known methods including, but not limited to, polypeptide A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification. See, e.g., Colligan, *Current Protocols in Immunology*, or *Current Protocols in Polypeptide Science*, John Wiley & Sons, NY, NY, (1997-2001), e.g., Chapters 1, 4, 6, 8, 9, 10, each entirely incorporated herein by reference.

CNGH0004 polypeptides and antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a eukaryotic host, including, for example, yeast, higher plant, insect and mammalian cells. 35 Depending upon the host employed in a recombinant production procedure, the polypeptide or antibody of the present invention can be glycosylated or can be non-glycosylated, with glycosylated preferred. Such methods are described in many standard laboratory manuals, such as Sambrook, *supra*,

- 5 Sections 17.37-17.42; Ausubel, *supra*, Chapters 10, 12, 13, 16, 18 and 20, Colligan, *Protein Science*, *supra*, Chapters 12-14, all entirely incorporated herein by reference.

#### CNGH0004 Polypeptides and Antibodies

The isolated polypeptides and antibodies of the present invention comprise at least one polypeptide and/or antibody amino acid sequence disclosed or described herein encoded by any suitable 10 polynucleotide, or any at least one isolated or prepared polypeptide antibody. Preferably, the at least one polypeptide has at least one CNGH0004 activity and the at least one antibody binds human CNGH0004 and, thereby partially or substantially modulates at least one structural or biological activity of at least one CNGH0004 polypeptide.

As used herein, the term "CNGH0004 polypeptide" refers to a polypeptide as described herein 15 that has at least one CNGH0004-dependent activity, such as 5-1000%, of the activity of a known or other CNGH0004 polypeptide or active portion thereof, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, or 1000% or more, depending on the assay. The capacity of a CNGH0004 polypeptide to have at least one CNGH0004-dependent activity is preferably assessed by at least one suitable 20 CNGH0004 polypeptide or receptor assay, as described herein and/or as known in the art.

As used herein, the term "neutralizing antibody" refers to an antibody that can inhibit at least one CNGH0004-dependent activity by about 5-1020%, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, or 1000% or more depending on the assay. The capacity of a CNGH0004 antibody to 25 inhibit an CNGH0004-dependent activity is preferably assessed by at least one suitable CNGH0004 polypeptide or receptor assay, as described herein and/or as known in the art. An antibody of the invention can be of any class (IgG, IgA, IgM, IgE, IgD, etc.) or isotype and can comprise a kappa or lambda light chain. In one embodiment, the human antibody comprises an IgG heavy chain or defined fragment, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4. Antibodies of this type can be 30 prepared by employing a transgenic mouse or other transgenic non-human mammal comprising at least one human light chain (e.g., combination of V, D and J regions) or heavy chain (e.g.,  $\gamma$ 1,  $\gamma$ 2,  $\gamma$ 3,  $\gamma$ 4,  $\mu$ 1,  $\alpha$ 1,  $\alpha$ 2,  $\delta$ ,  $\epsilon$ ) transgenes as described herein and/or as known in the art. In another embodiment, the human CNGH0004 human antibody comprises an IgG1 heavy chain and an IgG1 light chain.

At least one antibody of the invention binds at least one specified epitope specific to at least 35 one CNGH0004 polypeptide, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of the polypeptide, which epitope can optionally comprise at least one portion of at least one extracellular,

5 soluble, hydrophilic, external or cytoplasmic portion of the polypeptide. The at least one specified epitope can comprise any combination of at least one amino acid sequence of at least 1-3 amino acids to the entire specified portion of contiguous amino acids of the SEQ ID NO:1.

The at least one antibody of the present invention can preferably comprise at least one antigen-binding region that comprises at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one heavy chain variable region and/or at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one light chain variable region. In a particular embodiment, the polypeptide and antibody can have an antigen-binding region that comprises at least a portion of at least one heavy chain (HC) CDR (i.e., HC CDR1, HC CDR2 and/or HC CDR3) having the amino acid sequence of the corresponding HC CDRs 1, 2 and/or 15 3. In another particular embodiment, the antibody or antigen-binding portion or variant can have at least one antigen-binding region that comprises at least a portion of at least one light chain (LC) CDR (i.e., LC CDR1, LC CDR2 and/or LC CDR3). Such antibodies can be prepared by chemically joining together the various portions (e.g., CDRs, framework) of the antibody using conventional techniques, by preparing and expressing a (i.e., one or more) nucleic acid molecule that encodes the antibody using 20 conventional techniques of recombinant DNA technology or by using any other suitable method.

The CNGH0004 antibody can comprise at least one of a heavy or light chain variable region having a defined amino acid sequence. For example, in a preferred embodiment, the CNGH0004 antibody comprises at least one heavy chain variable region; and/or at least one light chain variable region. Antibodies that bind to human CNGH0004 and that comprise a defined heavy or light chain 25 variable region can be prepared using suitable methods, such as phage display (Katsube, Y., et al., *Int J Mol. Med.*, 1(5):863-868 (1998)) or methods that employ transgenic animals, as known in the art and/or as described herein. For example, a transgenic mouse, comprising a functionally rearranged human immunoglobulin heavy chain transgene and a transgene comprising DNA from a human immunoglobulin light chain locus that can undergo functional rearrangement, can be immunized with 30 human CNGH0004 or a fragment thereof to elicit the production of antibodies. If desired, the antibody producing cells can be isolated and hybridomas or other immortalized antibody-producing cells can be prepared as described herein and/or as known in the art. Alternatively, the antibody, specified portion or variant can be expressed using the encoding nucleic acid or portion thereof in a suitable host cell.

The invention also relates to antibodies, antigen-binding fragments, immunoglobulin chains 35 and CDRs comprising amino acids in a sequence that is substantially the same as an amino acid sequence described herein. Preferably, such antibodies or antigen-binding fragments and antibodies comprising such chains or CDRs can bind human CNGH0004 with high affinity (e.g., K<sub>D</sub> less than or

5 equal to about  $10^9$  M). Amino acid sequences that are substantially the same as the sequences described herein include sequences comprising conservative amino acid substitutions, as well as amino acid deletions and/or insertions. A conservative amino acid substitution refers to the replacement of a first amino acid by a second amino acid that has chemical and/or physical properties (e.g., charge, structure, polarity, hydrophobicity/hydrophilicity) that are similar to those of the first amino acid.

10 Conservative substitutions include replacement of one amino acid by another within the following groups: lysine (K), arginine (R) and histidine (H); aspartate (D) and glutamate (E); asparagine (N), glutamine (Q), serine (S), threonine (T), tyrosine (Y), K, R, H, D and E; alanine (A), valine (V), leucine (L), isoleucine (I), proline (P), phenylalanine (F), tryptophan (W), methionine (M), cysteine (C) and glycine (G); F, W and Y; C, S and T.

15 **Amino Acid Codes**

The amino acids that make up CNGH0004 polypeptides or antibodies of the present invention are often abbreviated. The amino acid designations can be indicated by designating the amino acid by its single letter code, its three letter code, name, or three nucleotide codon(s) as is well understood in the art (see Alberts, B., et al., Molecular Biology of The Cell, Third Ed., Garland Publishing, Inc., New

20 York, 1994):

SINGLE LETTER CODE	THREE LETTER CODE	NAME	THREE NUCLEOTIDE CODON(S)
A	Ala	Alanine	GCA, GCC, GCG, GCU
C	Cys	Cysteine	UGC, UGU
D	Asp	Aspartic acid	GAC, GAU
E	Glu	Glutamic acid	GAA, GAG
F	Phe	Phenylalanine	UUC, UUU
G	Gly	Glycine	GGA, GGC, GGG, GGU
H	His	Histidine	CAC, CAU
I	Ile	Isoleucine	AUA, AUC, AUU
K	Lys	Lysine	AAA, AAG
L	Leu	Leucine	UUA, UUG, CUA, CUC, CUG, CUU
M	Met	Methionine	AUG
N	Asn	Asparagine	AAC, AAU
P	Pro	Proline	CCA, CCC, CCG, CCU
Q	Gln	Glutamine	CAA, CAG
R	Arg	Arginine	AGA, AGG, CGA, CGC, CGG, CGU
S	Ser	Serine	AGC, AGU, UCA, UCC, UCG, UCU
T	Thr	Threonine	ACA, ACC, ACG, ACU
V	Val	Valine	GUA, GUC, GUG, GUU
W	Trp	Tryptophan	UGG

Y	Tyr	Tyrosine	UAC, UAU
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An CNGH0004 antibody of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein.

10 Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of amino acid substitutions, insertions or deletions for any given CNGH0004 antibody, fragment or variant will not be more than 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, such as 1-30 or any range or value therein, as specified herein:

15 Amino acids in an CNGH0004 antibody of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, *supra*, Chapters 8, 15; Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, such as, but not limited to at least one CNGH0004 neutralizing activity. Sites that are critical for antibody binding can also be 20 identified by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith, et al., *J. Mol. Biol.* 224:899-904 (1992) and de Vos, et al., *Science* 255:306-312 (1992)).

25 CNGH0004 polypeptides of the present invention can include, but are not limited to, at least one portion, sequence or combination selected from 3-100 to all of the contiguous amino acids of at least one of SEQ ID NO:1, such as but not limited to, 1-82, 83-259, 259-377, 378-433, 434-438, 438-493, 498-559, 1631-1685, 1690-1743, 1789-1842, 2021-2078, 2083-2141, 2146-2199, 2204-2259, 2264-2318, 2323-2376, 2381-2435, 2440-2493, 2498-2551, 2556-2608, 2660-2712, 2717-2770, 2775-2828, 2833-2886, 2891-2944, 2949-3002, 3007-3059, 3064-3117, 3122-3176, 3181-3236, 3241-3294, 3299-3352, 3357-3411, 3416-3468, 1231-1267, 1269-1305, 1307-1343, 1345-1381, 1383-1419, 1748-1784, 3468-3499, 3504-3531, 3536-3563, 1431-1623, 643-722, 561-642, 1196-1229, 727-787, 1847-30 1900, 1963-2016, 1905-1958, 999-1036, 1041-1106, 1108-1160, 1-41, or 305-360 of SEQ ID NO:1.

35 Non-limiting CDRs or portions of CNGH0004 polypeptides or antibodies of the invention that can enhance or maintain at least one of the listed activities include, but are not limited to, any of the above polypeptides, further comprising at least one mutation corresponding to at least one substitution selected from the group consisting of at least one of S249L, V507I, C842W, E980G, Y1063C, K1416Q, D1442V, A1810E.

5 An CNGH0004 polypeptide can further optionally comprise a polypeptide of at least one of 70-100% of the contiguous amino acids of at least one of SEQ ID NO:1 or any variant thereof.

In one embodiment, the amino acid sequence of a CNGH0004 polypeptide or antibody has about 70-100% identity (e.g., 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) to the amino acid sequence 10 of the corresponding chain of at least one of SEQ ID NO:1. Preferably, 70-100% amino acid identity (i.e., 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) is determined using a suitable computer algorithm, as known in the art.

The polypeptides and antibodies of the present invention, or specified variants thereof, can comprise any number of contiguous amino acid residues from an antibody of the present invention, 15 wherein that number is selected from the group of integers consisting of from 10-100% of the number of contiguous residues in a CNGH0004 polypeptide or antibody. Optionally, this subsequence of contiguous amino acids is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 or more amino acids in length, or any range or value 20 therein. Further, the number of such subsequences can be any integer selected from the group consisting of from 1 to 20, such as at least 2, 3, 4, or 5.

As those of skill will appreciate, the present invention includes at least one biologically active polypeptide or antibody of the present invention. Biologically active polypeptides or antibodies have a specific activity at least 20%, 30%, or 40%, and preferably at least 50%, 60%, or 70%, and most preferably at least 80%, 90%, or 95%-1000% of that of the native (non-synthetic), endogenous or related 25 and known polypeptide or antibody. Methods of assaying and quantifying measures of enzymatic activity and substrate specificity, are well known to those of skill in the art.

In another aspect, the invention relates to CNGH0004 polypeptides or antibodies of the invention, as described herein, which are modified by the covalent attachment of a moiety. Such modification can produce a CNGH0004 polypeptide or antibody with improved pharmacokinetic 30 properties (e.g., increased *in vivo* serum half-life). The organic moiety can be a linear or branched hydrophilic polymeric group, fatty acid group, or fatty acid ester group. In particular embodiments, the hydrophilic polymeric group can have a molecular weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g., polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrrolidone, and the fatty acid or fatty acid 35 ester group can comprise from about eight to about forty carbon atoms.

The modified polypeptides and antibodies of the invention can comprise one or more organic moieties that are covalently bonded, directly or indirectly, to the antibody or polypeptide. Each

5     organic moiety that is bonded to the polypeptide or antibody of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to an organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, a CNGH0004 antibody  
10   or polypeptide modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying antibodies or polypeptides of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like), carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine,  
15   polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrrolidone. Preferably, the hydrophilic polymer that modifies the polypeptide or antibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example PEG<sub>5000</sub> and PEG<sub>20,000</sub>, wherein the subscript is the average molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted  
20   with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (e.g., activated with N, N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

25     Fatty acids and fatty acid esters suitable for modifying antibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying antibodies of the invention include, for example, n-dodecanoate (C<sub>12</sub>, laurate), n-tetradecanoate (C<sub>14</sub>, myristate), n-octadecanoate (C<sub>18</sub>, stearate), n-eicosanoate (C<sub>20</sub>, arachidate), n-docosanoate (C<sub>22</sub>, behenate), n-triacontanoate (C<sub>30</sub>), n-tetracontanoate (C<sub>40</sub>), cis-Δ9-octadecanoate (C<sub>18</sub>, oleate), all cis-  
30   Δ5,8,11,14-eicosatetraenoate (C<sub>20</sub>, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably one to about six, carbon atoms.

35     The modified human polypeptides and antibodies can be prepared using suitable methods, such as by reaction with one or more modifying agents. A "modifying agent" as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty acid, a fatty acid ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that

- 5 can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acryloyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example a divalent C<sub>1</sub>-C<sub>12</sub> group wherein one or more carbon atoms can be replaced by a heteroatom such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, -(CH<sub>2</sub>)<sub>3</sub>-NH-(CH<sub>2</sub>)<sub>6</sub>-NH-, -(CH<sub>2</sub>)<sub>7</sub>-NH- and -CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-O-CH-NH-. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (e.g., mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for example, Thompson, et al., WO 92/16221 the entire teachings of which are incorporated herein by reference.)

Modified polypeptides or antibodies of the invention can be produced by reacting the polypeptide or antibody with a modifying agent. For example, the organic moieties can be bonded to the antibody or polypeptide in a non-site specific manner by employing an amine-reactive modifying agent, for example, an NHS ester of PEG. Modified CNGH0004 polypeptides or antibodies can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of the polypeptide and antibody. The reduced polypeptide and antibody can then be reacted with a thiol-reactive modifying agent to produce the modified antibody of the invention. Modified polypeptides and antibodies comprising an organic moiety that is bonded to specific sites of an antibody of the present invention can be prepared using suitable methods, such as reverse proteolysis (Fisch et al., *Bioconjugate Chem.*, 3:147-153 (1992); Werlen et al., *Bioconjugate Chem.*, 5:411-417 (1994); Kumaran et al., *Polypeptide Sci.* 6(10):2233-2241 (1997); Itoh et al., *Bioorg. Chem.*, 24(1): 59-68 (1996); Capellas et al.,

- 5 *Biotechnol. Bioeng.*, 56(4):456-463 (1997)), and the methods described in Hermanson, G. T.,  
10 *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).

#### ANTI-IDIOTYPE ANTIBODIES TO ANTI-CNGH0004 ANTIBODY COMPOSITIONS

In addition to monoclonal or chimeric CNGH0004 antibodies, the present invention is also directed to an idiotypic (Id) antibody specific for such antibodies of the invention. An anti-Id antibody is an antibody that recognizes unique determinants generally associated with the antigen-binding region of another antibody. The Id can be prepared by immunizing an animal of the same species and genetic type (e.g. mouse strain) as the source of the Id antibody with the antibody or a CDR containing region thereof. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody and produce an anti-Id antibody. The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-called anti-Id antibody.

#### CNGH0004 POLYPEPTIDE AND ANTIBODY COMPOSITIONS

The present invention also provides at least one CNGH0004 antibody or polypeptide composition comprising at least one, at least two, at least three, at least four, at least five, or at least 6-50, or any range or value therein, CNGH0004 antibodies or polypeptides thereof, as described herein. Such compositions can comprise 0.00001-99.9999 percent by weight, volume, concentration, molarity, or molality as liquid, gas, or dry solutions, mixtures, suspension, emulsions or colloids, as known in the art or as described herein, on any range or value therein, such as but not limited to 0.00001, 0.00003, 0.00005, 0.00009, 0.0001, 0.0003, 0.0005, 0.0009, 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 %. Such compositions of the present invention thus include but are not limited to 0.00001-100 mg/ml and/or 0.00001-100 mg/g.

The composition can optionally further comprise an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. Such drugs are well known in the art, including

- 5 formulations, indications, dosing and administration for each presented herein (see., e.g., *Nursing 2001 Handbook of Drugs*, 21<sup>st</sup> edition, Springhouse Corp., Springhouse, PA, 2001; *Health Professional's Drug Guide 2001*, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ; *Pharmacotherapy Handbook*, Wells et al., ed., Appleton & Lange, Stamford, CT, each entirely incorporated herein by reference).
- 10 The anti-infective drug can be at least one selected from amebicides or at least one antiprotozoals, anthelmintics, antifungals, antimarialials, antituberculotics or at least one antileprotics, aminoglycosides, penicillins, cephalosporins, tetracyclines, sulfonamides, fluoroquinolones, antivirals, macrolide anti-infectives, miscellaneous anti-infectives. The CV drug can be at least one selected from inotropics, antiarrhythmics, antianginals, antihypertensives, antilipemics, miscellaneous cardiovascular drugs.
- 15 The CNS drug can be at least one selected from nonnarcotic analgesics or at least one selected from antipyretics, nonsteroidal anti-inflammatory drugs, narcotic or at least one opioid analgesics, sedative-hypnotics, anticonvulsants, antidepressants, antianxiety drugs, antipsychotics, central nervous system stimulants, antiparkinsonians, miscellaneous central nervous system drugs. The ANS drug can be at least one selected from cholinergics (parasympathomimetics), anticholinergics, adrenergics (sympathomimetics), adrenergic blockers (sympatholytics), skeletal muscle relaxants, neuromuscular blockers. The respiratory tract drug can be at least one selected from antihistamines, bronchodilators, expectorants or at least one antitussives, miscellaneous respiratory drugs. The GI tract drug can be at least one selected from antacids or at least one adsorbents or at least one antiflatulents, digestive enzymes or at least one gallstone solubilizers, antidiarrheals, laxatives, antiemetics, antiulcer drugs.
- 20 The hormonal drug can be at least one selected from corticosteroids, androgens or at least one anabolic steroids, estrogens or at least one progestins, gonadotropins, antidiabetic drugs or at least one glucagon, thyroid hormones, thyroid hormone antagonists, pituitary hormones, parathyroid-like drugs. The drug for fluid and electrolyte balance can be at least one selected from diuretics, electrolytes or at least one replacement solutions, acidifiers or at least one alkalinizers. The hematologic drug can be at least one selected from hematinics, anticoagulants, blood derivatives, thrombolytic enzymes. The
- 25 antineoplastics can be at least one selected from alkylating drugs, antimetabolites, antibiotic antineoplastics, antineoplastics that alter hormone balance, miscellaneous antineoplastics. The immunomodulation drug can be at least one selected from immunosuppressants, vaccines or at least one toxoids, antitoxins or at least one antivenins, immune serums, biological response modifiers. The
- 30 ophthalmic, otic, and nasal drugs can be at least one selected from ophthalmic anti-infectives, ophthalmic anti-inflammatories, miotics, mydriatics, ophthalmic vasoconstrictors, miscellaneous ophthalmics, otics, nasal drugs. The topical drug can be at least one selected from local anti-infectives,
- 35

5 scabicides or at least one pediculicides, topical corticosteroids. The nutritional drug can be at least one selected from vitamins, minerals, or calorics. See, e.g., contents of *Nursing 2001 Drug Handbook, supra.*

The at least one amebicide or antiprotozoal can be at least one selected from atovaquone, chloroquine hydrochloride, chloroquine phosphate, metronidazole, metronidazole hydrochloride, 10 pentamidine isethionate. The at least one anthelmintic can be at least one selected from mebendazole, pyrantel pamoate, thiabendazole. The at least one antifungal can be at least one selected from amphotericin B, amphotericin B cholesteryl sulfate complex, amphotericin B lipid complex, amphotericin B liposomal, flucconazole, flucytosine, griseofulvin microsize, griseofulvin ultramicrosize, itraconazole, ketoconazole, nystatin, terbinafine hydrochloride. The at least one 15 antimarial can be at least one selected from chloroquine hydrochloride, chloroquine phosphate, doxycycline, hydroxychloroquine sulfate, mefloquine hydrochloride, primaquine phosphate, pyrimethamine, pyrimethamine with sulfadoxine. The at least one antituberculotic or antileprotic can be at least one selected from clofazimine, cycloserine, dapsone, ethambutol hydrochloride, isoniazid, 20 pyrazinamide, rifabutin, rifampin, rifapentine, streptomycin sulfate. The at least one aminoglycoside can be at least one selected from amikacin sulfate, gentamicin sulfate, neomycin sulfate, streptomycin sulfate, tobramycin sulfate. The at least one penicillin can be at least one selected from amoxicillin/clavulanate potassium, amoxicillin trihydrate, ampicillin, ampicillin sodium, ampicillin trihydrate, ampicillin sodium/sulbactam sodium, cloxacillin sodium, dicloxacillin sodium, mezlocillin sodium, naftillin sodium, oxacillin sodium, penicillin G benzathine, penicillin G potassium, penicillin 25 G procaine, penicillin G sodium, penicillin V potassium, piperacillin sodium, piperacillin sodium/tazobactam sodium, ticarcillin disodium, ticarcillin disodium/clavulanate potassium. The at least one cephalosporin can be at least one selected from at least one of cefaclor, cefadroxil, cefazolin sodium, cefdinir, cefepime hydrochloride, cefixime, cefmetazole sodium, cefonicid sodium, cefoperazone sodium, cefotaxime sodium, cefotetan disodium, cefoxitin sodium, cefpodoxime proxetil, 30 cefprozil, cestazidime, cestibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuroxime sodium, cephalexin hydrochloride, cephalexin monohydrate, cephadrine, loracarbef. The at least one tetracycline can be at least one selected from demeclocycline hydrochloride, doxycycline calcium, doxycycline hyclate, doxycycline hydrochloride, doxycycline monohydrate, minocycline hydrochloride, tetracycline hydrochloride. The at least one sulfonamide can be at least one selected from co-trimoxazole, sulfadiazine, sulfamethoxazole, sulfisoxazole, sulfisoxazole acetyl. The at least 35 one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin,

- 5 trovafloxacin mesylate. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin mesylate. The at least one antiviral can be at least one selected from abacavir sulfate, acyclovir sodium, amantadine hydrochloride, amprenavir, cidofovir, delavirdine mesylate, didanosine, efavirenz, famciclovir, fomivirsen sodium, foscarnet sodium, ganciclovir, indinavir sulfate, lamivudine, lamivudine/zidovudine, nelfinavir mesylate, nevirapine; oseltamivir phosphate, ribavirin, rimantadine hydrochloride, ritonavir, saquinavir, saquinavir mesylate, stavudine, valacyclovir hydrochloride, zalcitabine, zanamivir, zidovudine. The at least one macroline anti-infective can be at least one selected from azithromycin, clarithromycin, dirithromycin, erythromycin base, erythromycin estolate, erythromycin ethylsuccinate, erythromycin lactobionate, erythromycin stearate. The at least one miscellaneous anti-infective can be at least one selected from aztreonam, bacitracin, chloramphenicol sodium succinate, clindamycin hydrochloride, clindamycin palmitate hydrochloride, clindamycin phosphate, imipenem and cilastatin sodium, meropenem, nitrofurantoin macrocrystals, nitrofurantoin microcrystals, quinupristin/dalfopristin, spectinomycin hydrochloride, trimethoprim, vancomycin hydrochloride. (See, e.g., pp. 24-214 of
- 10 20 *Nursing 2001 Drug Handbook.*
- The at least one inotropic can be at least one selected from amrinone lactate, digoxin, milrinone lactate. The at least one antiarrhythmic can be at least one selected from adenosine, amiodarone hydrochloride, atropine sulfate, bretylium tosylate, diltiazem hydrochloride, disopyramide, disopyramide phosphate, esmolol hydrochloride, flecainide acetate, ibutilide fumarate, lidocaine
- 15 25 hydrochloride, mexiletine hydrochloride, moricizine hydrochloride, phenytoin, phenytoin sodium, procainamide hydrochloride, propafenone hydrochloride, propranolol hydrochloride, quinidine bisulfate, quinidine gluconate, quinidine polygalacturonate, quinidine sulfate, sotalol, tocainide hydrochloride, verapamil hydrochloride. The at least one antianginal can be at least one selected from amlodipine besylate, amyl nitrite, bepridil hydrochloride, diltiazem hydrochloride, isosorbide
- 30 35 dinitrate, isosorbide mononitrate, nadolol, nicardipine hydrochloride, nifedipine, nitroglycerin, propranolol hydrochloride, verapamil, verapamil hydrochloride. The at least one antihypertensive can be at least one selected from acebutolol hydrochloride, amlodipine besylate, atenolol, benazepril hydrochloride, betaxolol hydrochloride, bisoprolol fumarate, candesartan cilexetil, captopril, carteolol hydrochloride, carvedilol, clonidine, clonidine hydrochloride, diazoxide, diltiazem hydrochloride, doxazosin mesylate, enalaprilat, enalapril maleate, eprosartan mesylate, felodipine, fenoldopam mesylate, fosinopril sodium, guanabenz acetate, guanadrel sulfate, guanfacine hydrochloride, hydralazine hydrochloride, irbesartan, isradipine, labetalol hydrochloride, lisinopril, losartan potassium,

- 5        methyldopa, methyldopate hydrochloride, metoprolol succinate, metoprolol tartrate, minoxidil, moexipril hydrochloride, nadolol, nicardipine hydrochloride, nifedipine, nisoldipine, nitroprusside sodium, penbutolol sulfate, perindopril erbumine, phentolamine mesylate, pindolol, prazosin hydrochloride, propranolol hydrochloride, quinapril hydrochloride, ramipril, telmisartan, terazosin hydrochloride, timolol maleate, trandolapril, valsartan, verapamil hydrochloride. The at least one  
10      antilipemic can be at least one selected from atorvastatin calcium, cerivastatin sodium, cholestyramine, colestipol hydrochloride, fenofibrate (micronized), fluvastatin sodium, gemfibrozil, lovastatin, niacin, pravastatin sodium; simvastatin. The at least one miscellaneous CV drug can be at least one selected from abciximab, alprostadil, arbutamine hydrochloride, cilostazol, clopidogrel bisulfate, dipyridamole, eptifibatide, midodrine hydrochloride, pentoxifylline, ticlopidine hydrochloride, tirofiban  
15      hydrochloride. (See, e.g., pp. 215-336 of *Nursing 2001 Drug Handbook*.)  
          The at least one nonnarcotic analgesic or antipyretic can be at least one selected from acetaminophen, aspirin, choline magnesium trisalicylate, disflunisal, magnesium salicylate. The at least one nonsteroidal anti-inflammatory drug can be at least one selected from celecoxib, diclofenac potassium, diclofenac sodium, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin,  
20      indomethacin sodium trihydrate, ketoprofen, ketorolac tromethamine, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, sulindac. The at least one narcotic or opioid analgesic can be at least one selected from alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, codeine phosphate, codeine sulfate, fentanyl citrate, fentanyl transdermal system, fentanyl transmucosal, hydromorphone hydrochloride, meperidine hydrochloride, methadone hydrochloride,  
25      morphine hydrochloride, morphine sulfate, morphine tartrate, nalbuphine hydrochloride, oxycodone hydrochloride, oxycodone pectinate, oxymorphone hydrochloride, pentazocine hydrochloride, pentazocine hydrochloride and naloxone hydrochloride, pentazocine lactate, propoxyphene hydrochloride, propoxyphene napsylate, remifentanil hydrochloride, sufentanil citrate, tramadol hydrochloride. The at least one sedative-hypnotic can be at least one selected from chloral hydrate, estazolam, flurazepam hydrochloride, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, temazepam, triazolam, zaleplon, zolpidem tartrate. The at least one  
30      anticonvulsant can be at least one selected from acetazolamide sodium, carbamazepine, clonazepam, clorazepate dipotassium, diazepam, divalproex sodium, ethosuximide, fosphenytoin sodium, gabapentin, lamotrigine, magnesium sulfate, phenobarbital, phenobarbital sodium, phenytoin, phenytoin sodium, phenytoin sodium (extended), primidone, tiagabine hydrochloride, topiramate, valproate sodium, valproic acid. The at least one antidepressant can be at least one selected from amitriptyline hydrochloride, amitriptyline pamoate, amoxapine, bupropion hydrochloride, citalopram

- 5 hydrobromide, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, imipramine hydrochloride, imipramine pamoate, mirtazapine, nefazodone hydrochloride, nortriptyline hydrochloride, paroxetine hydrochloride, phenelzine sulfate, sertraline hydrochloride, tranylcypromine sulfate, trimipramine maleate, venlafaxine hydrochloride. The at least one antianxiety drug can be at least one selected from alprazolam, buspirone hydrochloride,
- 10 chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam, doxepin hydrochloride, hydroxyzine embonate, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam, mephobarbital, midazolam hydrochloride, oxazepam. The at least one antipsychotic drug can be at least one selected from chlorpromazine hydrochloride, clozapine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, haloperidol, haloperidol decanoate, haloperidol lactate, loxapine hydrochloride, loxapine succinate, mesoridazine besylate, molindone hydrochloride, olanzapine, perphenazine, pimozide, prochlorperazine, quetiapine fumarate, risperidone, thioridazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine hydrochloride. The at least one central nervous system stimulant can be at least one selected from amphetamine sulfate, caffeine, dextroamphetamine sulfate, doxapram hydrochloride, methamphetamine hydrochloride,
- 15 methylphenidate hydrochloride, modafinil, pemoline, phentermine hydrochloride. The at least one antiparkinsonian can be at least one selected from amantadine hydrochloride, benztrapine mesylate, biperiden hydrochloride, biperiden lactate, bromocriptine mesylate, carbidopa-levodopa, entacapone, levodopa, pergolide mesylate, pramipexole dihydrochloride, ropinirole hydrochloride, selegiline hydrochloride, tolcapone, trihexyphenidyl hydrochloride. The at least one miscellaneous central nervous system drug can be at least one selected from bupropion hydrochloride, donepezil hydrochloride, droperidol, fluvoxamine maleate, lithium carbonate, lithium citrate, naratriptan hydrochloride, nicotine polacrilex, nicotine transdermal system, propofol, rizatriptan benzoate, sibutramine hydrochloride monohydrate, sumatriptan succinate, tacrine hydrochloride, zolmitriptan.
- (See, e.g., pp. 337-530 of *Nursing 2001 Drug Handbook*.)
- 20 The at least one cholinergic (e.g., parasympathomimetic) can be at least one selected from bethanechol chloride, edrophonium chloride, neostigmine bromide, neostigmine methylsulfate, physostigmine salicylate, pyridostigmine bromide. The at least one anticholinergics can be at least one selected from atropine sulfate, dicyclomine hydrochloride, glycopyrrolate, hyoscyamine, hyoscyamine sulfate, propantheline bromide, scopolamine, scopolamine butylbromide, scopolamine hydrobromide.
- 25 The at least one adrenergics (sympathomimetics) can be at least one selected from dobutamine hydrochloride, dopamine hydrochloride, metaraminol bitartrate, norepinephrine bitartrate, phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate. The at least

5 one adrenergic blocker (sympatholytic) can be at least one selected from dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, propranolol hydrochloride. The at least one skeletal muscle relaxant can be at least one selected from baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine hydrochloride, dantrolene sodium, methocarbamol, tizanidine hydrochloride. The at least one neuromuscular blockers can be at least one selected from atracurium besylate, cisatracurium besylate, 10 doxacurium chloride, mivacurium chloride, pancuronium bromide, pipecuronium bromide, rapacuronium bromide, rocuronium bromide, succinylcholine chloride, tubocurarine chloride, vecuronium bromide. (See, e.g., pp. 531-84 of *Nursing 2001 Drug Handbook*.)

The at least one antihistamine can be at least one selected from brompheniramine maleate, cetirizine hydrochloride, chlorpheniramine maleate, clemastine fumarate, cyproheptadine hydrochloride, diphenhydramine hydrochloride, fexofenadine hydrochloride, loratadine, promethazine hydrochloride, promethazine theoclinate, triprolidine hydrochloride. The at least one bronchodilators can be at least one selected from albuterol, albuterol sulfate, aminophylline, atropine sulfate, ephedrine sulfate, epinephrine, epinephrine bitartrate, epinephrine hydrochloride, ipratropium bromide, isoproterenol, isoproterenol hydrochloride, isoproterenol sulfate, levalbuterol hydrochloride, 20 metaproterenol sulfate, oxtriphylline, pирbutерол acetate, salmeterol xinafoate, terbutaline sulfate, theophylline. The at least one expectorants or antitussives can be at least one selected from benzonatate, codeine phosphate, codeine sulfate, dextromethorphan hydrobromide, diphenhydramine hydrochloride, guaifenesin, hydromorphone hydrochloride. The at least one miscellaneous respiratory drug can be at least one selected from acetylcysteine, beclomethasone dipropionate, beractant, 25 budesonide, calfactant, cromolyn sodium, dornase alfa, epoprostenol sodium, flunisolide, fluticasone propionate, montelukast sodium, nedocromil sodium, palivizumab, triamcinolone acetonide, zafirlukast, zileuton. (See, e.g., pp. 585-642 of *Nursing 2001 Drug Handbook*.)

The at least one antacid, adsorbents, or antiflatulents can be at least one selected from aluminum carbonate, aluminum hydroxide, calcium carbonate, magaldrate, magnesium hydroxide, 30 magnesium oxide, simethicone, sodium bicarbonate. The at least one digestive enzymes or gallstone solubilizers can be at least one selected from pancreatin, pancrelipase, ursodiol. The at least one antidiarrheal can be at least one selected from attapulgite, bismuth subsalicylate, calcium polycarbophil, diphenoxylate hydrochloride or atropine sulfate, loperamide, octreotide acetate, opium tincture, opium tincture (camphorated). The at least one laxative can be at least one selected from bisacodyl, calcium polycarbophil, cascara sagrada, cascara sagrada aromatic fluidextract, cascara sagrada fluidextract, castor oil, docusate calcium, docusate sodium, glycerin, lactulose, magnesium citrate, magnesium hydroxide, magnesium sulfate, methylcellulose, mineral oil, polyethylene glycol or

- 5 electrolyte solution, psyllium, senna, sodium phosphates. The at least one antiemetic can be at least one selected from chlorpromazine hydrochloride, dimenhydrinate, dolasetron mesylate, dronabinol, granisetron hydrochloride, meclizine hydrochloride, metoclopramide hydrochloride, ondansetron hydrochloride, perphenazine, prochlorperazine, prochlorperazine edisylate, prochlorperazine maleate, promethazine hydrochloride, scopolamine, thiethylperazine maleate, trimethobenzamide hydrochloride.

10 The at least one antiulcer drug can be at least one selected from cimetidine, cimetidine hydrochloride, famotidine, lansoprazole, misoprostol, nizatidine, omeprazole, rabeprazole sodium, rantidine bismuth citrate, ranitidine hydrochloride, sucralfate. (See, e.g., pp. 643-95 of *Nursing 2001 Drug Handbook*.)

The at least one corticosteroids can be at least one selected from betamethasone, betamethasone

- 15 acetate or beclamethasone sodium phosphate, betamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, fludrocortisone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate. The at least one androgen or anabolic steroids can be at least one selected from danazol, fluoxymesterone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, testosterone, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone transdermal system. The at least one estrogen or progestin can be at least one selected from esterified estrogens, estradiol, estradiol cypionate, estradiol/norethindrone acetate transdermal system, estradiol valerate, estrogens (conjugated), estropipate, ethinyl estradiol, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and levonorgestrel, ethinyl estradiol and norethindrone, ethinyl estradiol and norethindrone acetate, ethinyl estradiol and norgestimate, ethinyl estradiol and norgestrel, ethinyl estradiol and norethindrone and acetate and ferrous fumarate, levonorgestrel, medroxyprogesterone acetate, mestranol and norethindron, norethindrone, norethindrone acetate, norgestrel, progesterone. The at least one gonadotropin can be at least one selected from ganirelix acetate, gonadoreline acetate, histrelin acetate, menotropins. The at least one antidiabetic or glucose can be at least one selected from acarbose, chlorpropamide, glimepiride, glipizide, glucagon, glyburide, insulins, metformin hydrochloride, miglitol, pioglitazone hydrochloride, repaglinide, rosiglitazone maleate, troglitazone. The at least one thyroid hormone can be at least one selected from levothyroxine sodium, liothyronine sodium, liotrix, thyroid. The at least one thyroid hormone antagonist can be at least one

5 selected from methimazole, potassium iodide, potassium iodide (saturated solution), propylthiouracil, radioactive iodine (sodium iodide  $^{131}\text{I}$ ), strong iodine solution. The at least one pituitary hormone can be at least one selected from corticotropin, cosyntropin, desmopressin acetate, leuproide acetate, repository corticotropin, somatrem, somatropin, vasopressin. The at least one parathyroid-like drug can be at least one selected from calcifediol, calcitonin (human), calcitonin (salmon), calcitriol, dihydrotachysterol, etidronate disodium. (See, e.g., pp. 696-796 of *Nursing 2001 Drug Handbook*.)

10 The at least one diuretic can be at least one selected from acetazolamide, acetazolamide sodium, amiloride hydrochloride, bumetanide, chlorothalidone, ethacrylate sodium, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, mannitol, metolazone, spironolactone, torsemide, triamterene, urea. The at least one electrolyte or replacement solution can be at least one selected from 15 calcium acetate, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, calcium lactate, calcium phosphate (dibasic), calcium phosphate (tribasic), dextran (high-molecular-weight), dextran (low-molecular-weight), hetastarch, magnesium chloride, magnesium sulfate, potassium acetate, potassium bicarbonate, potassium chloride, potassium gluconate, Ringer's injection, Ringer's injection (lactated), sodium chloride. The at least one acidifier 20 or alkalinizer can be at least one selected from sodium bicarbonate, sodium lactate, tromethamine. (See, e.g., pp. 797-833 of *Nursing 2001 Drug Handbook*.)

The at least one hematinic can be at least one selected from ferrous fumarate, ferrous gluconate, ferrous sulfate, ferrous sulfate (dried), iron dextran, iron sorbitol, polysaccharide-iron complex, sodium ferric gluconate complex. The at least one anticoagulant can be at least one selected 25 from ardeparin sodium, dalteparin sodium, danaparoid sodium, enoxaparin sodium, heparin calcium, heparin sodium, warfarin sodium. The at least one blood derivative can be at least one selected from albumin 5%, albumin 25%, antihemophilic factor, anti-inhibitor coagulant complex, antithrombin III (human), factor IX (human), factor IX complex, plasma protein fractions. The at least one 30 thrombolytic enzyme can be at least one selected from alteplase, anistreplase, reteplase (recombinant), streptokinase, urokinase. (See, e.g., pp. 834-66 of *Nursing 2001 Drug Handbook*.)

The at least one alkylating drug can be at least one selected from busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, ifosfamide, lomustine, mechlorethamine hydrochloride; melphalan, melphalan hydrochloride, streptozocin, temozolamide, thiotepa. The at least one antimetabolite can be at least one selected from capecitabine, cladribine, cytarabine, floxuridine, 35 fludarabine phosphate, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, methotrexate sodium, thioguanine. The at least one antibiotic antineoplastic can be at least one selected from bleomycin sulfate, dactinomycin, daunorubicin citrate liposomal, daunorubicin hydrochloride, doxorubicin

- 5 hydrochloride, doxorubicin hydrochloride liposomal, epirubicin hydrochloride, idarubicin hydrochloride, mitomycin, pentostatin, plicamycin, valrubicin. The at least one antineoplastics that alter hormone balance can be at least one selected from anastrozole, bicalutamide, estramustine phosphate sodium, exemestane, flutamide, goserelin acetate, letrozole, leuproreotide acetate, megestrol acetate, nilutamide, tamoxifen citrate, testolactone, toremifene citrate. The at least one miscellaneous 10 antineoplastic can be at least one selected from asparaginase, bacillus Calmette-Guerin (BCG) (live intravesical), dacarbazine, docetaxel, etoposide, etoposide phosphate, gemcitabine hydrochloride, irinotecan hydrochloride, mitotane, mitoxantrone hydrochloride, paclitaxel, pegaspargase, porfimer sodium, procarbazine hydrochloride, rituximab, teniposide, topotecan hydrochloride, trastuzumab, tretinoin, vinblastine sulfate, vincristine sulfate, vinorelbine tartrate. (See, e.g., pp. 867-963 of *Nursing* 15 *2001 Drug Handbook*.)

The at least one immunosuppressant can be at least one selected from azathioprine, basiliximab, cyclosporine, daclizumab, lymphocyte immune globulin, muromonab-CD3, mycophenolate mofetil, mycophenolate mofetil hydrochloride, sirolimus, tacrolimus. The at least one vaccine or toxoid can be at least one selected from BCG vaccine, cholera vaccine, diphtheria and tetanus toxoids (adsorbed), diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, diphtheria and tetanus toxoids and whole-cell pertussis vaccine, *Haemophilus b* conjugate vaccines, hepatitis A vaccine (inactivated), hepatitis B vaccine (recombinant), influenza virus vaccine 1999-2000 trivalent types A & B (purified surface antigen), influenza virus vaccine 1999-2000 trivalent types A & B (subvirion or purified subvirion), influenza virus vaccine 1999-2000 trivalent types A & B (whole virion), Japanese encephalitis virus vaccine (inactivated), Lyme disease vaccine (recombinant OspA), measles and mumps and rubella virus vaccine (live), measles and mumps and rubella virus vaccine (live attenuated), measles virus vaccine (live attenuated), meningococcal polysaccharide vaccine, mumps virus vaccine (live), plague vaccine, pneumococcal vaccine (polyvalent), poliovirus vaccine (inactivated), poliovirus vaccine (live, oral, trivalent), rabies vaccine (adsorbed), rabies vaccine (human diploid cell), rubella and mumps virus vaccine (live), rubella virus vaccine (live, attenuated), tetanus toxoid (adsorbed), tetanus toxoid (fluid), typhoid vaccine (oral), typhoid vaccine (parenteral), typhoid Vi polysaccharide vaccine, varicella virus vaccine, yellow fever vaccine. The at least one antitoxin or antivenin can be at least one selected from black widow spider antivenin, *Crotalidae* antivenom (polyvalent), diphtheria antitoxin (equine), *Micruurus fulvius* antivenin). The at least one immune serum can be at least one selected from cytomegalovirus immune globulin (intravenous), hepatitis B immune globulin (human), immune globulin intramuscular, immune globulin intravenous, rabies immune globulin (human), respiratory syncytial virus immune globulin intravenous (human), Rh<sub>0</sub>(D)

5 immune globulin (human), Rb<sub>b</sub>(D) immune globulin intravenous (human), tetanus immune globulin (human), varicella-zoster immune globulin. The at least one biological response modifiers can be at least one selected from aldesleukin, epoetin alfa, filgrastim, glatiramer acetate for injection, interferon alfacon-1, interferon alfa-2a (recombinant), interferon alfa-2b (recombinant), interferon beta-1a, interferon beta-1b (recombinant), interferon gamma-1b, levamisole hydrochloride, oprelvekin, sargramostim. (See, e.g., pp. 964-1040 of *Nursing 2001 Drug Handbook*.)

10 The at least one ophthalmic anti-infectives can be selected form bacitracin, chloramphenicol, ciprofloxacin hydrochloride, erythromycin, gentamicin sulfate, ofloxacin 0.3%, polymyxin B sulfate, sulfacetamide sodium 10%, sulfacetamide sodium 15%, sulfacetamide sodium 30%, tobramycin, vidarabine. The at least one ophthalmic anti-inflammatories can be at least one selected from dexamethasone, dexamethasone sodium phosphate, diclofenac sodium 0.1%, fluorometholone, flurbiprofen sodium, ketorolac tromethamine, prednisolone acetate (suspension) prednisolone sodium phosphate (solution). The at least one miotic can be at least one selected from acetylcholine chloride, carbachol (intraocular), carbachol (topical), echothiopate iodide, pilocarpine, pilocarpine hydrochloride, pilocarpine nitrate. The at least one mydriatic can be at least one selected from atropine sulfate, cyclopentolate hydrochloride, epinephrine hydrochloride, epinephryl borate, homatropine hydrobromide, phenylephrine hydrochloride, scopolamine hydrobromide, tropicamide. The at least one ophthalmic vasoconstrictors can be at least one selected from naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride. The at least one miscellaneous ophthalmics can be at least one selected from apraclonidine hydrochloride, betaxolol hydrochloride, brimonidine tartrate, carteolol hydrochloride, dipivefrin hydrochloride, dorzolamide hydrochloride, emedastine difumarate, fluorescein sodium, ketotifen fumarate, latanoprost, levobunolol hydrochloride, metipranolol hydrochloride, sodium chloride (hypertonic), timolol maleate. The at least one otic can be at least one selected from boric acid, carbamide peroxide, chloramphenicol, triethanolamine polypeptide oleate-condensate. The at least one nasal drug can be at least one selected from beclomethasone dipropionate, budesonide, ephedrine sulfate, epinephrine hydrochloride, flunisolide, fluticasone propionate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, triamcinolone acetonide, xylometazoline hydrochloride. (See, e.g., pp. 1041-97 of *Nursing 2001 Drug Handbook*.)

15 The at least one local anti-infectives can be at least one selected from acyclovir, amphotericin B, azelaic acid cream, bacitracin, butoconazole nitrate, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamicin sulfate, ketoconazole, mafenide acetate, metronidazole (topical), miconazole nitrate, mupirocin, naftifine hydrochloride, neomycin sulfate, nitrofurazone, nystatin, silver

- 5 sulfadiazine, terbinafine hydrochloride, terconazole, tetracycline hydrochloride, tioconazole, tolnaftate. The at least one scabicide or pediculicide can be at least one selected from crotamiton, lindane, permethrin, pyrethrins. The at least one topical corticosteroid can be at least one selected from betamethasone dipropionate, betamethasone valerate, clobetasol propionate, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, diflorasone diacetate, fluocinolone acetonide, fluocinonide, flurandrenolide, fluticasone propionate, halcione, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocorisone valerate, mometasone furoate, triamcinolone acetonide. (See, e.g., pp. 1098-1136 of *Nursing 2001 Drug Handbook*.)
- The at least one vitamin or mineral can be at least one selected from vitamin A, vitamin B complex, cyanocobalamin, folic acid, hydroxocobalamin, leucovorin calcium, niacin, niacinamide, pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, vitamin C, vitamin D, cholecalciferol, ergocalciferol, vitamin D analogue, doxercalciferol, paricalcitol, vitamin E, vitamin K analogue, phytonadione, sodium fluoride, sodium fluoride (topical), trace elements, chromium, copper, iodine, manganese, selenium, zinc. The at least one calories can be at least one selected from amino acid infusions (crystalline), amino acid infusions in dextrose, amino acid infusions with electrolytes, amino acid infusions with electrolytes in dextrose, amino acid infusions for hepatic failure, amino acid infusions for high metabolic stress, amino acid infusions for renal failure, dextrose, fat emulsions, medium-chain triglycerides. (See, e.g., pp. 1137-63 of *Nursing 2001 Drug Handbook*.)

CNGH0004 antibody or polypeptide compositions of the present invention can further comprise at least one of any suitable and/or effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 protein or antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy, optionally further comprising at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-I or TBP-II), nerelimonimab, infliximab, enteracept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomolate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a

5 thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a theophylline, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Non-limiting examples of such cytokines include, but are not limited to, any of IL-1 to IL-23. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., *Pharmacotherapy Handbook*, 2<sup>nd</sup> Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

Such compositions can also include toxin molecules that are associated, bound, co-formulated or co-administered with at least one antibody or polypeptide of the present invention. The toxin can optionally act to selectively kill the pathologic cell or tissue. The pathologic cell can be a cancer or other cell. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g., selected from at least one of ricin, diphtheria toxin, a venom toxin, or a bacterial toxin. The term toxin also includes both endotoxins and exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), Staphylococcal enterotoxin A (SEA), B (SEB), or C (SEC), Streptococcal enterotoxins and the like. Such bacteria include, but are not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype O157:H7), Staphylococcus species (e.g., *Staphylococcus aureus*, *Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi*, *Salmonella cholera-suis*, *Salmonella enteritidis*), *Clostridium* species (e.g., *Clostridium perfringens*, *Clostridium difficile*, *Clostridium botulinum*), *Camphlobacter* species (e.g., *Camphlobacter jejuni*, *Camphlobacter fetus*), *Helicobacter* species, (e.g., *Helicobacter pylori*), *Aeromonas* species (e.g., *Aeromonas sobria*, *Aeromonas hydrophila*, *Aeromonas caviae*), *Plesiomonas*

- 5 *shigelloides*, *Yersina enterocolitica*, *Vibrios* species (e.g., *Vibrios cholerae*, *Vibrios parahaemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed., INTERNAL MEDICINE, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., Bacterial Infections of Humans: Epidemiology and Control, 2d. Ed., pp 239-254, Plenum Medical Book Co., New York (1991); Mandell et al, Principles and Practice of Infectious Diseases, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, FEMS Microbiology Immunology, 76:121-134 (1991); Marrack et al, Science, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference.
- 10 CNGH0004 antibody or polypeptide compounds, compositions or combinations of the present invention can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like.

- 15 Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but limited to, Gennaro, Ed., *Remington's Pharmaceutical Sciences*, 18<sup>th</sup> Edition, Mack Publishing Co. (Easton, PA) 1990.
- 20 Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the CNGH0004 antibody or polypeptide composition as well known in the art or as described herein.

- 25 Pharmaceutical excipients and additives useful in the present composition include but are not limited to polypeptides, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditol, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume.
- Exemplary but non-limiting polypeptide excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative 30 amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. One preferred amino acid is glycine.

- Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; 35 disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditol, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. Preferred carbohydrate

5 excipients for use in the present invention are mannitol, trehalose, and raffinose.

CNGH0004 antibody or polypeptide compositions can also include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the present compositions are organic acid salts such as citrate.

10 Additionally, CNGH0004 antibody or polypeptide compositions of the invention can include polymeric excipients/additives such as polyvinylpyrrolidones, ficsols (a polymeric sugar), dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl- $\beta$ -cyclodextrin), polyethylene glycols, flavoring agents, 15 antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as "TWEEN 20" and "TWEEN 80"), lipids (e.g., phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

These and additional known pharmaceutical excipients and/or additives suitable for use in the CNGH0004 antibody or polypeptide compositions according to the invention are known in the art, e.g., 20 as listed in "Remington: The Science & Practice of Pharmacy", 19<sup>th</sup> ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52<sup>nd</sup> ed., Medical Economics, Montvale, NJ (1998), the disclosures of which are entirely incorporated herein by reference. Preferred carrier or excipient materials are carbohydrates (e.g., saccharides and alditols) and buffers (e.g., citrate) or polymeric agents.

## 25 Formulations

As noted above, the invention provides for stable formulations, which is preferably a phosphate buffer with saline or a chosen salt, as well as preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising at least one CNGH0004 antibody or polypeptide in a pharmaceutically acceptable formulation. Preserved formulations contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9,

- 5    2.0, 2.1, 2.2, 2.3; 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5,  
4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-  
2% m-cresol (e.g., 0.2, 0.3, 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1, 1.5, 1.9, 2.0,  
2.5%), 0.001-0.5% thimerosal (e.g., 0.005, 0.01), 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9,  
1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01,  
1.0%, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.
- 10   0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

As noted above, the invention provides an article of manufacture, comprising packaging material and at least one vial comprising a solution of at least one CNGH0004 antibody or polypeptide with the prescribed buffers and/or preservatives, optionally in an aqueous diluent, wherein said packaging material comprises a label that indicates that such solution can be held over a period of 15 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further comprises an article of manufacture, comprising packaging material, a first vial comprising lyophilized at least one CNGH0004 antibody or polypeptide, and a second vial comprising an aqueous diluent of prescribed buffer or preservative, wherein said packaging material comprises a label that instructs a patient to reconstitute the at least one CNGH0004 antibody or polypeptide in the aqueous diluent to 20 form a solution that can be held over a period of twenty-four hours or greater.

The at least one CNGH0004 antibody or polypeptide used in accordance with the present invention can be produced by recombinant means, including from mammalian cell or transgenic preparations, or can be purified from other biological sources, as described herein or as known in the art.

25   The range of at least one CNGH0004 antibody in at least one product of the present invention includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 ng/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

30   The range of at least one CNGH0004 antibody in at least one product of the present invention includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0  $\mu$ g/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

35   Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and

5 the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the formulation is a concentration sufficient to yield an microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

10 Other excipients, e.g. isotonicity agents, buffers, antioxidants, preservative enhancers, can be optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 6.0 to about 8.0. Preferably the formulations of the present invention have pH between about 6.8 and 15 about 7.8. Preferred buffers include phosphate buffers, most preferably sodium phosphate, particularly phosphate buffered saline (PBS).

20 Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyols, other block copolymers, and chelators such as EDTA and EGTA can optionally be added to the formulations or compositions to reduce aggregation. These additives are particularly useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable 25 surfactant mitigates the propensity for the polypeptide to aggregate.

30 The formulations of the present invention can be prepared by a process which comprises mixing at least one CNGH0004 antibody or polypeptide and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at least one 35 CNGH0004 antibody or polypeptide and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one CNGH0004 antibody or polypeptide in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide the polypeptide and preservative at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can

- 5 be optimized for the concentration and means of administration used.

The claimed formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or polypeptide that is reconstituted with a second vial containing water, a preservative and/or excipients, preferably a phosphate buffer and/or saline and a chosen salt, in an aqueous diluent. Either a single solution vial or dual vial 10 requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus can provide a more convenient treatment regimen than currently available.

The present claimed articles of manufacture are useful for administration over a period of immediately to twenty-four hours or greater. Accordingly, the presently claimed articles of manufacture offer significant advantages to the patient. Formulations of the invention can optionally be 15 safely stored at temperatures of from about 2 to about 40°C and retain the biologically activity of the polypeptide for extended periods of time, thus, allowing a package label indicating that the solution can be held and/or used over a period of 6, 12, 18, 24, 36, 48, 72, or 96 hours or greater. If preserved diluent is used, such label can include use up to 1-12 months, one-half, one and a half, and/or two years.

20 The solutions of at least one CNGH0004 antibody or polypeptide in the invention can be prepared by a process that comprises mixing at least one antibody or polypeptide in an aqueous diluent. Mixing is carried out using conventional dissolution and mixing procedures. To prepare a suitable diluent, for example, a measured amount of at least one antibody or polypeptide in water or buffer is combined in quantities sufficient to provide the polypeptide and optionally a preservative or 25 buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed products can be provided to patients as clear solutions or as dual vials 30 comprising a vial of lyophilized at least one CNGH0004 antibody or polypeptide that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

The claimed products can be provided indirectly to patients by providing to 35 pharmacies, clinics, or other such institutions and facilities, clear solutions or dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or polypeptide that is reconstituted with a second vial containing the aqueous diluent. The clear solution in this case can be up to one liter or even larger

- 5 in-size, providing a large reservoir from which smaller portions of the at least one antibody or polypeptide solution can be retrieved one or multiple times for transfer into smaller vials and provided by the pharmacy or clinic to their customers and/or patients.

Recognized devices comprising these single vial systems include those pen-injector devices for delivery of a solution such as BD Pens, BD Autojector<sup>®</sup>, Humaject<sup>®</sup>, NovoPen<sup>®</sup>, B-D<sup>®</sup>Pen, 10 AutoPen<sup>®</sup>, and OptiPen<sup>®</sup>, GenotropinPen<sup>®</sup>, Genotronorm Pen<sup>®</sup>, Humatro Pen<sup>®</sup>, Reco-Pen<sup>®</sup>, Roferon Pen<sup>®</sup>, Biojector<sup>®</sup>, iject<sup>®</sup>, J-tip Needle-Free Injector<sup>®</sup>, Inraject<sup>®</sup>, Medi-Ject<sup>®</sup>, e.g., as made or developed by Becton Dickensen (Franklin Lakes, NJ, [www.bectondickenson.com](http://www.bectondickenson.com)), Disetronic (Burgdorf, Switzerland, [www.disetronic.com](http://www.disetronic.com); Bioject, Portland, Oregon ([www.bioject.com](http://www.bioject.com)); National Medical Products, Weston Medical (Peterborough, UK, [www.weston-medical.com](http://www.weston-medical.com)), Medi-Ject Corp (Minneapolis, MN, [www.mediject.com](http://www.mediject.com)). Recognized devices comprising a dual vial system include those pen-injector systems for reconstituting a lyophilized drug in a cartridge for delivery of the reconstituted solution such as the HumatroPen<sup>®</sup>.

The products presently claimed include packaging material. The packaging material provides, in addition to the information required by the regulatory agencies, the conditions under which 20 the product can be used. The packaging material of the present invention provides instructions to the patient to reconstitute the at least one CNGH0004 antibody or polypeptide in the aqueous diluent to form a solution and to use the solution over a period of 2-24 hours or greater for the two vial, wet/dry, product. For the single vial, solution product, the label indicates that such solution can be used over a period of 2-24 hours or greater. The presently claimed products are useful for human pharmaceutical 25 product use.

The formulations of the present invention can be prepared by a process that comprises mixing at least one CNGH0004 antibody or polypeptide and a selected buffer, preferably a phosphate buffer containing saline or a chosen salt. Mixing the at least one antibody or polypeptide and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a 30 suitable formulation, for example, a measured amount of at least one antibody or polypeptide in water or buffer is combined with the desired buffering agent in water in quantities sufficient to provide the polypeptide and buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all 35 factors that can be optimized for the concentration and means of administration used.

The claimed stable or preserved formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or

5. polypeptide that is reconstituted with a second vial containing a preservative or buffer and excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

10 At least one CNGH0004 antibody or polypeptide in either the stable or preserved formulations or solutions described herein, can be administered to a patient in accordance with the present invention via a variety of delivery methods including SC or IM injection; transdermal, pulmonary, transmucosal, implant, osmotic pump, cartridge, micro pump, or other means appreciated by the skilled artisan, as well-known in the art.

#### Therapeutic Applications

15 The present invention also provides a method for modulating or treating at least one CNGH0004 related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one antibody or polypeptide of the present invention.

The present invention also provides a method for modulating or treating at least one CNGH0004 related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at 20 least one of obesity, an immune related disease, a cardiovascular disease, an infectious disease, a malignant disease or a neurologic disease.

The present invention also provides a method for modulating or treating at least one adult or pediatric immune or inflammation related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of, or at least one inflammation related to, rheumatoid arthritis, juvenile 25 rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, antiphospholipid syndrome, iridocyclitis, uveitis, optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis, Wegener's granulomatosis, sarcoidosis, orchitis, vasectomy or vasectomy reversal procedures, allergic atopic 30 diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, trauma, hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, 35 rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, type I or type II diabetes, nephrosis, atopic diseases, hypersensitivity

- 5 reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphylaxis, dermatitis, pernicious anemia, hemolytic disease, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, receptor hypersensitivity reactions, chronic obstructive pulmonary disease (COPD), Graves disease, Raynaud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-mediated cytotoxicity, gene therapy inflammation (e.g., adenovirus, AAV, vaccinia, DNA or RNA, Muloney murine leukemia virus (MMLV) and the like),
- 10 type III hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary biliary cirrhosis, vitiligo,
- 15 vasculitis, post-MI cardiotomy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic, idiopathic, Wilson's disease, hemachromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, Hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease,
- 20 chronic obstructive pulmonary disease (COPD), familial hematophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, okt3 therapy, cd3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited to asthenia, anemia, cachexia, and the like), chronic salicylate intoxication, and the like. See, e.g., the Merck Manual, 12th-17th Editions,
- 25 Merck & Company, Rahway, NJ (1972, 1977, 1982, 1987, 1992, 1999), Pharmacotherapy Handbook, Wells et al., eds., Second Edition, Appleton and Lange, Stamford, Conn. (1998, 2000), each entirely incorporated by reference.

The present invention also provides a method for modulating or treating at least one cardiovascular disease in a cell, tissue, organ, animal, or patient, including, but not limited to, at least one of cardiac stun syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic atherosclerotic disease, hypertension, arterial hypertension, renovascular hypertension, syncope, shock, syphilis of the cardiovascular system,

- 5 heart failure, cor pulmonale, primary pulmonary hypertension, cardiac arrhythmias, atrial ectopic beats, atrial flutter, atrial fibrillation (sustained or paroxysmal), post perfusion syndrome, cardiopulmonary bypass inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrhythmias, ventricular fibrillation, His bundle arrhythmias, atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery disease, angina pectoris,
- 10 myocardial infarction, cardiomyopathy, dilated congestive cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial disease, cardiac tumors, aortic and peripheral aneurysms, aortic dissection, inflammation of the aorta, occlusion of the abdominal aorta and its branches, peripheral vascular disorders, occlusive arterial disorders, peripheral atherosclerotic disease, thromboangiitis obliterans, functional peripheral arterial disorders, Raynaud's phenomenon and disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula, lymphedema, lipedema, unstable angina, reperfusion injury, post pump syndrome, ischemia-reperfusion injury, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

The present invention also provides a method for modulating or treating at least one infectious disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: acute or chronic infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection, HIV neuropathy, meningitis, hepatitis (A,B or C, or the like), septic arthritis, peritonitis, pneumonia, epiglottitis, e. coli 0157:h7, hemolytic uremic syndrome, thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii pneumonia, pelvic inflammatory disease, orchitis, epididymitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemophagocytic syndrome, vital encephalitis, aseptic meningitis, and the like. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g., selected from at least one of diphtheria toxin, a venom toxin, a viral toxin or a bacterial toxin. The term toxin also includes both endotoxins and exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), Staphylococcal

- 5 enterotoxin A (SEA), B (SEB), or C (SEC), Streptococcal enterotoxins anthrax endotoxin, and the like. Such bacteria include, but are not limited to, gram negative or gram positive bacteria, *Bacillus*, *E. coli*, *Streptococcus*, *Staphylococcus*, *Shigella*, *Salmonella*, *Clostridium*, *Campylobacter*, *Heliobacter*, *Aeromonas*, *Enterococcus*, *Pseudomonas*, and the like, such as but not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype 0157:H7),
- 10 *Staphylococcus* species (e.g., *Staphylococcus aureus*, *Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi*, *Salmonella cholera-suis*, *Salmonella enteritidis*), *Clostridium* species (e.g., *Clostridium perfringens*, *Clostridium difficile*, *Clostridium botulinum*), *Campylobacter* species (e.g., *Campylobacter jejuni*, *Campylobacter fetus*), *Heliobacter* species, (e.g., *Heliobacter pylori*),
- 15 *Aeromonas* species (e.g., *Aeromonas sobria*, *Aeromonas hydrophila*, *Aeromonas caviae*), *Plesiomonas shigelloides*, *Yersina enterocolitica*, *Vibrios* species (e.g., *Vibrios cholerae*, *Vibrios parahaemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed., INTERNAL MEDICINE, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., Bacterial Infections of Humans: Epidemiology and Control, 2d. Ed., pp 239-254, Plenum Medical Book Co.,
- 20 New York (1991); Mandell et al, Principles and Practice of Infectious Diseases, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, FEMS Microbiology Immunology, 76:121-134 (1991); Marrack et al, Science, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference. Such a method can optionally comprise administering an effective amount of a composition
- 25 or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

The present invention also provides a method for modulating or treating at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), acute myelogenous leukemia, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head cancer, neck cancer, hereditary nonpolyposis cancer, Hodgkin's lymphoma, liver cancer, lung cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma,

- 5 testicular cancer, adenocarcinomas, sarcomas, malignant melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, and the like.

Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

- 10 The present invention also provides a method for modulating or treating at least one neurologic disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or 15 cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranucleo Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, 20 Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Reisnu's disease, abetalipoproteinemia, ataxia, telangiectasia, and mitochondrial multi-system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit' such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's 25 Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallervorden-Spatz disease; and Dementia pugilistica, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. See, e.g., the Merck Manual, 16<sup>th</sup> 30 Edition, Merck & Company, Rahway, NJ (1992).

- Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.
- 35 Such a method can optionally further comprise co-administration or combination therapy for treating such diseases, wherein the administering of said at least one CNGH0004 antibody or polypeptide, specified portion or variant thereof, further comprises administering, before concurrently, and/or after,

5 at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-I or TBP-II), nerelimonmab, infliximab, entercept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin,  
10 aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a  
15 fluroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an  
20 immuno-suppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Suitable  
25 dosages are well known in the art. See, e.g., Wells et al., eds., *Pharmacotherapy Handbook*, 2<sup>nd</sup> Edition, Appleton and Lange, Stamford, CT (2000); PDR *Pharmacopoeia*, Tarascon Pocket *Pharmacopoeia* 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

TNF antagonists suitable for compositions, combination therapy, co-administration, devices  
30 and/or methods of the present invention (further comprising at least one anti body, specified portion and variant thereof, of the present invention), include, but are not limited to, TNF antibodies, antigen-binding fragments thereof, and receptor molecules which bind specifically to TNF; compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, such as thalidomide, tenidap, phosphodiesterase inhibitors (e.g., pentoxifylline and rolipram), A2b adenosine receptor  
35 agonists and A2b adenosine receptor enhancers; compounds which prevent and/or inhibit TNF receptor signalling, such as mitogen activated polypeptide (MAP) kinase inhibitors; compounds which block and/or inhibit membrane TNF cleavage, such as metallopolypeptidase inhibitors; compounds which

- 5 block and/or inhibit TNF activity, such as angiotensin converting enzyme (ACE) inhibitors (e.g., captopril), and compounds which block and/or inhibit TNF production and/or synthesis, such as MAP kinase inhibitors.

As used herein, a "tumor necrosis factor antibody," "TNF antibody," "TNF $\alpha$  antibody," or fragment and the like decreases, blocks, inhibits, abrogates or interferes with TNF $\alpha$  activity *in vitro*, *in situ* and/or preferably *in vivo*. For example, a suitable TNF human antibody of the present invention can bind TNF $\alpha$  and includes TNF antibodies, antigen-binding fragments thereof, and specified mutants or domains thereof that bind specifically to TNF $\alpha$ . A suitable TNF antibody or fragment can also decrease, block, abrogate, interfere, prevent and/or inhibit TNF RNA, DNA or polypeptide synthesis, TNF release, TNF receptor signaling, membrane TNF cleavage, TNF activity, TNF production and/or synthesis.

Chimeric antibody cA2 consists of the antigen binding variable region of the high-affinity neutralizing mouse human TNF $\alpha$  IgG1 antibody, designated A2, and the constant regions of a human IgG1, kappa immunoglobulin. The human IgG1 Fc region improves allogeneic antibody effector function, increases the circulating serum half-life and decreases the immunogenicity of the antibody.

20 The avidity and epitope specificity of the chimeric antibody cA2 is derived from the variable region of the murine antibody A2. In a particular embodiment, a preferred source for nucleic acids encoding the variable region of the murine antibody A2 is the A2 hybridoma cell line.

Chimeric A2 (cA2) neutralizes the cytotoxic effect of both natural and recombinant human TNF $\alpha$  in a dose dependent manner. From binding assays of chimeric antibody cA2 and recombinant human TNF $\alpha$ , the affinity constant of chimeric antibody cA2 was calculated to be  $1.04 \times 10^{10} M^{-1}$ . Preferred methods for determining monoclonal antibody specificity and affinity by competitive inhibition can be found in Harlow, *et al.*, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1988; Colligan *et al.*, eds., *Current Protocols in Immunology*, Greene Publishing Assoc. and Wiley Interscience, New York, (1992-2000); Kozbor *et al.*, *Immunol. Today*, 4:72-79 (1983); Ausubel *et al.*, eds. *Current Protocols in Molecular Biology*, Wiley Interscience, New York (1987-2000); and Muller, *Meth. Enzymol.*, 92:589-601 (1983), which references are entirely incorporated herein by reference.

In a particular embodiment, murine monoclonal antibody A2 is produced by a cell line designated c134A. Chimeric antibody cA2 is produced by a cell line designated c168A.

35 Additional examples of monoclonal TNF antibodies that can be used in the present invention are described in the art (see, e.g., U.S. Patent No. 5,231,024; Möller, A. *et al.*, *Cytokine* 2(3):162-169 (1990); U.S. Application No. 07/943,852 (filed September 11, 1992); Rathjen *et al.*, International

- 5 Publication No. WO 91/02078 (published February 21, 1991); Rubin *et al.*, EPO Patent Publication  
No. 0 218 868 (published April 22, 1987); Yone *et al.*, EPO Patent Publication No. 0 288 088 (October  
26, 1988); Liang, *et al.*, *Biochem. Biophys. Res. Comm.* 137:847-854 (1986); Meager, *et al.*,  
*Hybridoma* 6:305-311 (1987); Fendly *et al.*, *Hybridoma* 6:359-369 (1987); Bringman, *et al.*,  
*Hybridoma* 6:489-507 (1987); and Hirai, *et al.*, *J. Immunol. Meth.* 96:57-62 (1987), which references  
10 are entirely incorporated herein by reference).

#### TNF Receptor Molecules

Preferred TNF receptor molecules useful in the present invention are those that bind TNF $\alpha$  with high affinity (see, e.g., Feldmann *et al.*, International Publication No. WO 92/07076 (published April 30, 1992); Schall *et al.*, *Cell* 61:361-370 (1990); and Loetscher *et al.*, *Cell* 61:351-359 (1990);  
15 which references are entirely incorporated herein by reference) and optionally possess low immunogenicity. In particular, the 55 kDa (p55 TNF-R) and the 75 kDa (p75 TNF-R) TNF cell surface receptors are useful in the present invention. Truncated forms of these receptors, comprising the extracellular domains (ECD) of the receptors or functional portions thereof (see, e.g., Corcoran *et al.*, *Eur. J. Biochem.* 223:831-840 (1994)), are also useful in the present invention. Truncated forms of the  
20 TNF receptors, comprising the ECD, have been detected in urine and serum as 30 kDa and 40 kDa TNF $\alpha$  inhibitory binding polypeptides (Engelmann, H. *et al.*, *J. Biol. Chem.* 265:1531-1536 (1990)). TNF receptor multimeric molecules and TNF immunoreceptor fusion molecules, and derivatives and fragments or portions thereof, are additional examples of TNF receptor molecules which are useful in the methods and compositions of the present invention. The TNF receptor molecules which can be  
25 used in the invention are characterized by their ability to treat patients for extended periods with good to excellent alleviation of symptoms and low toxicity. Low immunogenicity and/or high affinity, as well as other undefined properties, can contribute to the therapeutic results achieved.

TNF receptor multimeric molecules useful in the present invention comprise all or a functional portion of the ECD of two or more TNF receptors linked via one or more polypeptide linkers or other  
30 nonpeptide linkers, such as polyethylene glycol (PEG). The multimeric molecules can further comprise a signal peptide of a secreted polypeptide to direct expression of the multimeric molecule. These multimeric molecules and methods for their production have been described in U.S. Application No. 08/437,533 (filed May 9, 1995), the content of which is entirely incorporated herein by reference.

TNF immunoreceptor fusion molecules useful in the methods and compositions of the present invention comprise at least one portion of one or more immunoglobulin molecules and all or a functional portion of one or more TNF receptors. These immunoreceptor fusion molecules can be assembled as monomers, or hetero- or homo-multimers. The immunoreceptor fusion molecules can

- 5 also be monovalent or multivalent. An example of such a TNF immunoreceptor fusion molecule is TNF receptor/IgG fusion polypeptide. TNF immunoreceptor fusion molecules and methods for their production have been described in the art (Lesslauer *et al.*, *Eur. J. Immunol.* 21:2883-2886 (1991); Ashkenazi *et al.*, *Proc. Natl. Acad. Sci. USA* 88:10535-10539 (1991); Peppé *et al.*, *J. Exp. Med.* 174:1483-1489 (1991); Kolls *et al.*, *Proc. Natl. Acad. Sci. USA* 91:215-219 (1994); Butler *et al.*,
- 10 *Cytokine* 6(6):616-623 (1994); Baker *et al.*, *Eur. J. Immunol.* 24:2040-2048 (1994); Beutler *et al.*, U.S. Patent No. 5,447,851; and U.S. Application No. 08/442,133 (filed May 16, 1995), each of which references are entirely incorporated herein by reference). Methods for producing immunoreceptor fusion molecules can also be found in Capon *et al.*, U.S. Patent No. 5,116,964; Capon *et al.*, U.S. Patent No. 5,225,538; and Capon *et al.*, *Nature* 337:525-531 (1989), which references are entirely
- 15 incorporated herein by reference.

A functional equivalent, derivative, fragment or region of TNF receptor molecule refers to the portion of the TNF receptor molecule, or the portion of the TNF receptor molecule sequence which encodes TNF receptor molecule, that is of sufficient size and sequences to functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF? with high affinity and possess low immunogenicity). A functional equivalent of TNF receptor molecule also includes modified TNF receptor molecules that functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF? with high affinity and possess low immunogenicity). For example, a functional equivalent of TNF receptor molecule can contain a "SILENT" codon or one or more amino acid substitutions, deletions or additions (e.g., substitution of one acidic amino acid for another acidic amino acid; or substitution of one codon encoding the same or different hydrophobic amino acid for another codon encoding a hydrophobic amino acid). See Ausubel *et al.*, *Current Protocols in Molecular Biology*, Greene Publishing Assoc. and Wiley-Interscience, New York (1987-2000).

Cytokines include any known cytokine. See, e.g., CopewithCytokines.com. Cytokine antagonists include, but are not limited to, any antibody, fragment or mimetic, any soluble receptor, fragment or mimetic, any small molecule antagonist, or any combination thereof.

**Therapeutic Treatments.** Any method of the present invention can comprise a method for treating a CNGH0004 mediated disorder or disease, comprising administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such disorders or diseases, wherein the administering of said at least one CNGH0004 antibody or

- 5 polypeptide, further comprises administering, before concurrently, and/or after, at least one selected from at least one at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluoroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine); an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist.
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**Polypeptide Dosing**

- 25 Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one CNGH0004 polypeptide composition that total, on average, a range from at least about 0.001 ng to 500 milligrams of at least one CNGH0004 polypeptide per kilogram of patient per dose, and preferably from at least about 0.1 ng to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition.
- 30 Alternatively, the effective serum concentration can comprise 0.0001ng –0.05 mg/ml serum concentration per single or multiple administration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, i.e., repeated individual
- 35 administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

5 Preferred doses of at least one polypeptide can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 micrograms or  
10 milligrams/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 20, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5, 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 ng or  $\mu$ g/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

20 Alternatively, the dosage administered can vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1  $\mu$ g to 100 milligrams per kilogram of body weight. Ordinarily 0.0001 to 50, and preferably 0.001 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.  
25

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100  $\mu$ g/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000 or 3000  $\mu$ g/kg, 30 per day, or 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or repeated doses.

5 Dosage forms (composition) suitable for internal administration generally contain from about 0.00001 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-99.999% by weight based on the total weight of the composition.

10 Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one CNGH0004 antibody composition that total, on average, a range from at least about 0.00001 to 500 milligrams of at least one CNGH0004 antibody per kilogram of patient per dose, and preferably from at least about 0.0001 to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition.

15 Alternatively, the effective serum concentration can comprise 0.0001-500 µg/ml serum concentration per single or multiple administration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, i.e., repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired

20 daily dose or effect is achieved.

#### Antibody Dosing

Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one CNGH0004 antibody composition that total, on average, a range from at least about 0.001 ng to 500 milligrams of at least one CNGH0004 antibody per kilogram of patient per dose, and preferably from at least about 0.1 ng to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition.

25 Alternatively, the effective serum concentration can comprise 0.0001ng - 0.05 mg/ml serum concentration per single or multiple administration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, i.e., repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

Preferred doses of at least one antibody can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 35 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64; 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87,

- 5 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 mg/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 20, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5,
- 10 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500; and/or 5000 µg/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.1 to 50, and preferably 0.1 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, or alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or repeated doses.

Dosage forms (composition) suitable for internal administration generally contain from about 0.1 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-99.999% by weight based on the total weight of the composition.

### 35 Administration

For parenteral administration, the antibody or polypeptide can be formulated as a solution, suspension, emulsion or lyophilized powder in association, or separately provided, with a

5 pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 1-10% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by known or suitable techniques.

10 Suitable pharmaceutical carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

#### Alternative Administration

15 Many known and developed modes of can be used according to the present invention for administering pharmaceutically effective amounts of at least one CNGH0004 antibody according to the present invention. While pulmonary administration is used in the following description, other modes of administration can be used according to the present invention with suitable results.

CNGH0004 antibodies of the present invention can be delivered in a carrier, as a solution, emulsion, colloid, or suspension, or as a dry powder, using any of a variety of devices and methods suitable for administration by inhalation or other modes described here within or known in the art.

#### 20 Parenteral Formulations and Administration

Formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for injection can be a non-toxic, non-orally administrable diluting agent such as aqueous solution or a sterile injectable solution or suspension in a solvent. As the usable vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent, or suspending solvent, sterile involatile oil can be used. For these purposes, any kind of involatile oil and fatty acid can be used, including natural or synthetic or semisynthetic fatty oils or fatty acids; natural or synthetic or semisynthetic mono- or di- or tri-glycerides. Parental administration is known in the art and includes, but is not limited to, conventional means of injections, a gas pressured needle-less injection device as described in U.S. Pat. No. 5,851,198, and a laser perforator device as described in U.S. Pat. No. 5,839,446 entirely incorporated herein by reference.

#### 35 Alternative Delivery

The invention further relates to the administration of at least one CNGH0004 antibody by parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic,

- 5 intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means. At least one CNGH0004 antibody composition can be prepared for use for parenteral (subcutaneous, intramuscular or intravenous) or any other administration particularly in the form of liquid solutions or suspensions; for use in vaginal or  
10 rectal administration particularly in semisolid forms such as, but not limited to, creams and suppositories; for buccal, or sublingual administration such as, but not limited to, in the form of tablets or capsules; or intranasally such as, but not limited to, the form of powders, nasal drops or aerosols or certain agents; or transdermally such as not limited to a gel, ointment, lotion, suspension or patch delivery system with chemical enhancers such as dimethyl sulfoxide to either modify the skin structure  
15 or to increase the drug concentration in the transdermal patch (Junginger, et al. In "Drug Permeation Enhancement"; Hsieh, D. S., Eds., pp. 59-90 (Marcel Dekker, Inc. New York 1994, entirely incorporated herein by reference), or with oxidizing agents that enable the application of formulations containing polypeptides and peptides onto the skin (WO 98/53847), or applications of electric fields to create transient transport pathways such as electroporation, or to increase the mobility of charged drugs  
20 through the skin such as iontophoresis, or application of ultrasound such as sonophoresis (U.S. Pat. Nos. 4,309,989 and 4,767,402) (the above publications and patents being entirely incorporated herein by reference).

#### Pulmonary/Nasal Administration

For pulmonary administration, preferably at least one CNGH0004 antibody composition is delivered in a particle size effective for reaching the lower airways of the lung or sinuses. According to the invention, at least one CNGH0004 antibody can be delivered by any of a variety of inhalation or nasal devices known in the art for administration of a therapeutic agent by inhalation. These devices capable of depositing aerosolized formulations in the sinus cavity or alveoli of a patient include metered dose inhalers, nebulizers, dry powder generators, sprayers, and the like. Other devices suitable for directing the pulmonary or nasal administration of antibodies are also known in the art. All such devices can use of formulations suitable for the administration for the dispensing of antibody in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non aqueous) or solid particles. Metered dose inhalers like the Ventolin<sup>®</sup> metered dose inhaler, typically use a propellant gas and require actuation during inspiration (See, e.g., WO 94/16970, WO 98/35888). Dry powder inhalers like Turbuhaler<sup>TM</sup> (Astra), Rotahaler<sup>®</sup> (Glaxo), Diskus<sup>®</sup> (Glaxo), Spiros<sup>TM</sup> inhaler (Dura), devices marketed by Inhale Therapeutics, and the Spinhaler<sup>®</sup> powder inhaler (Fisons), use breath-actuation of a mixed powder (US 4668218 Astra, EP 237507 Astra, WO 97/25086 Glaxo, WO  
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5 94/08552 Dura, US 5458135 Inhale, WO 94/06498 Fisons, entirely incorporated herein by reference). Nebulizers like AERx™ Aradigm, the Ultravent® nebulizer (Mallinckrodt), and the Acorn II® nebulizer (Marquest Medical Products) (US 5404871 Aradigm, WO 97/22376), the above references entirely incorporated herein by reference, produce aerosols from solutions, while metered dose inhalers, dry powder inhalers, etc. generate small particle aerosols. These specific examples of commercially  
10 available inhalation devices are intended to be a representative of specific devices suitable for the practice of this invention, and are not intended as limiting the scope of the invention. Preferably, a composition comprising at least one CNGH0004 antibody is delivered by a dry powder inhaler or a sprayer. There are several desirable features of an inhalation device for administering at least one antibody of the present invention. For example, delivery by the inhalation device is advantageously  
15 reliable, reproducible, and accurate. The inhalation device can optionally deliver small dry particles, e.g. less than about 10 µm, preferably about 1-5 µm, for good respirability.

#### Administration of CNGH0004 antibody Compositions as a Spray

A spray including CNGH0004 antibody composition can be produced by forcing a suspension or solution of at least one CNGH0004 antibody through a nozzle under pressure. The nozzle size and configuration, the applied pressure, and the liquid feed rate can be chosen to achieve the desired output and particle size. An electrospray can be produced, for example, by an electric field in connection with a capillary or nozzle feed. Advantageously, particles of at least one CNGH0004 antibody composition delivered by a sprayer have a particle size less than about 10 µm, preferably in the range of about 1 µm to about 5 µm, and most preferably about 2 µm to about 3 µm.

25 Formulations of at least one CNGH0004 polypeptide or antibody composition suitable for use with a sprayer typically include antibody or polypeptide compositions in an aqueous solution at a concentration of about 0.0000001 mg to about 1000 mg of at least one CNGH0004 antibody or polypeptide composition per ml of solution or mg/gm, or any range or value therein, e.g., but not limited to, .1, .2, .3, .4, .5, .6, .7, .8, .9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22,  
30 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 ng or µg or mg/ml or ng or µg or mg/gm. The formulation can include agents such as an excipient, a buffer, an isotonicity agent; a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the antibody composition, such as a buffer, a reducing agent, a bulk polypeptide, or a carbohydrate. Bulk polypeptides useful in formulating antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating antibody compositions include sucrose, mannitol, lactose, trehalose, glucose, or the like. The antibody composition formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the antibody or

- 5 polypeptide composition caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbitol fatty acid esters. Amounts will generally range between 0.001 and 14% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan monooleate, polysorbate 80, polysorbate 20, or the like. Additional agents  
10 known in the art for formulation of a polypeptide such as CNGH0004 antibodies, or specified portions or variants, can also be included in the formulation.

**Administration of CNGH0004 antibody compositions by a Nebulizer**

Antibody composition can be administered by a nebulizer, such as jet nebulizer or an ultrasonic nebulizer. Typically, in a jet nebulizer, a compressed air source is used to create a high-  
15 velocity air jet through an orifice. As the gas expands beyond the nozzle, a low-pressure region is created, which draws a solution of antibody composition through a capillary tube connected to a liquid reservoir. The liquid stream from the capillary tube is sheared into unstable filaments and droplets as it exits the tube, creating the aerosol. A range of configurations, flow rates, and baffle types can be employed to achieve the desired performance characteristics from a given jet nebulizer. In an  
20 ultrasonic nebulizer, high-frequency electrical energy is used to create vibrational, mechanical energy, typically employing a piezoelectric transducer. This energy is transmitted to the formulation of antibody composition either directly or through a coupling fluid, creating an aerosol including the antibody composition. Advantageously, particles of antibody composition delivered by a nebulizer have a particle size less than about 10  $\mu\text{m}$ , preferably in the range of about 1  $\mu\text{m}$  to about 5  $\mu\text{m}$ , and  
25 most preferably about 2  $\mu\text{m}$  to about 3  $\mu\text{m}$ .

Formulations of at least one CNGH0004 antibody suitable for use with a nebulizer, either jet or ultrasonic, typically include a concentration of about 0.1 mg to about 100 mg of at least one CNGH0004 antibody polypeptide per ml of solution. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The  
30 formulation can also include an excipient or agent for stabilization of the at least one CNGH0004 antibody composition, such as a buffer, a reducing agent, a bulk polypeptide, or a carbohydrate. Bulk polypeptides useful in formulating at least one CNGH0004 antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating at least one CNGH0004 antibody include sucrose, mannitol, lactose, trehalose, glucose, or the like. The at least one CNGH0004  
35 antibody formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the at least one CNGH0004 antibody caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid

5 esters and alcohols, and polyoxyethylene sorbital fatty acid esters. Amounts will generally range between 0.001 and 4% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan mono-oleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a polypeptide such as antibody polypeptide can also be included in the formulation.

10 **Administration of CNGH0004 antibody compositions By A Metered Dose Inhaler**

In a metered dose inhaler (MDI), a propellant, at least one CNGH0004 antibody, and any excipients or other additives are contained in a canister as a mixture including a liquefied compressed gas. Actuation of the metering valve releases the mixture as an aerosol, preferably containing particles in the size range of less than about 10  $\mu\text{m}$ , preferably about 1  $\mu\text{m}$  to about 5  $\mu\text{m}$ , and most preferably about 2  $\mu\text{m}$  to about 3  $\mu\text{m}$ . The desired aerosol particle size can be obtained by employing a formulation of antibody composition produced by various methods known to those of skill in the art, including jet-milling, spray drying, critical point condensation, or the like. Preferred metered dose inhalers include those manufactured by 3M or Glaxo and employing a hydrofluorocarbon propellant.

Formulations of at least one CNGH0004 antibody for use with a metered-dose inhaler device will generally include a finely divided powder containing at least one CNGH0004 antibody as a suspension in a non-aqueous medium, for example, suspended in a propellant with the aid of a surfactant. The propellant can be any conventional material employed for this purpose, such as chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol and 1,1,1,2-tetrafluoroethane, HFA-134a (hydrofluoroalkane-134a), HFA-227 (hydrofluoroalkane-227), or the like. Preferably the propellant is a hydrofluorocarbon. The surfactant can be chosen to stabilize the at least one CNGH0004 antibody as a suspension in the propellant, to protect the active agent against chemical degradation, and the like. Suitable surfactants include sorbitan trioleate, soya lecithin, oleic acid, or the like. In some cases solution aerosols are preferred using solvents such as ethanol. Additional agents known in the art for formulation of a polypeptide such as polypeptide can also be included in the formulation.

One of ordinary skill in the art will recognize that the methods of the current invention can be achieved by pulmonary administration of at least one CNGH0004 antibody compositions via devices not described herein.

35 **Oral Formulations and Administration**

Formulations for oral rely on the co-administration of adjuvants (e.g., resorcinols and nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase

- 5 artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylo) to inhibit enzymatic degradation. The active constituent compound of the solid-type dosage form for oral administration can be mixed with at least one additive, including sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectins, gum  
10 tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, and glyceride. These dosage forms can also contain other type(s) of additives, e.g., inactive diluting agent, lubricant such as magnesium stearate, paraben, preserving agent such as sorbic acid, ascorbic acid, alpha-tocopherol, antioxidant such as cysteine, disintegrator, binder, thickener, buffering agent, sweetening agent, flavoring agent, perfuming agent, etc.
- 15 Tablets and pills can be further processed into enteric-coated preparations. The liquid preparations for oral administration include emulsion, syrup, elixir, suspension and solution preparations allowable for medical use. These preparations can contain inactive diluting agents ordinarily used in said field, e.g., water. Liposomes have also been described as drug delivery systems for insulin and heparin (U.S. Pat. No. 4,239,754). More recently, microspheres of artificial polymers  
20 of mixed amino acids (polypeptideoids) have been used to deliver pharmaceuticals (U.S. Pat. No. 4,925,673). Furthermore, carrier compounds described in U.S. Pat. No. 5,879,681 and U.S. Pat. No. 5,871,753 are used to deliver biologically active agents orally are known in the art.

#### Mucosal Formulations and Administration

- For absorption through mucosal surfaces, compositions and methods of administering at least one CNGH0004 antibody include an emulsion comprising a plurality of submicron particles, a mucoadhesive macromolecule, a bioactive peptide, and an aqueous continuous phase, which promotes absorption through mucosal surfaces by achieving mucoadhesion of the emulsion particles (U.S. Pat. Nos. 5,514,670). Mucous surfaces suitable for application of the emulsions of the present invention can include corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal routes of administration. Formulations for vaginal or rectal administration, e.g., suppositories, can contain as excipients, for example, polyalkyleneglycols, vaseline, cocoa butter, and the like. Formulations for intranasal administration can be solid and contain as excipients, for example, lactose or can be aqueous or oily solutions of nasal drops. For buccal administration excipients include sugars, calcium stearate, magnesium stearate, pregelatinated starch, and the like (U.S. Pat. Nos.  
30 5,849,695).

#### Transdermal Formulations and Administration

For transdermal administration, the at least one CNGH0004 antibody is encapsulated in a

5 delivery device such as a liposome or polymeric nanoparticles, microparticle, microcapsule, or microspheres (referred to collectively as microparticles unless otherwise stated). A number of suitable devices are known, including microparticles made of synthetic polymers such as polyhydroxy acids such as polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, and polyphosphazenes, and natural polymers such as collagen, polyamino acids, albumin and other 10 polypeptides, alginate and other polysaccharides, and combinations thereof (U.S. Pat. Nos. 5,814,599).

#### 10 Prolonged Administration and Formulations

It can be sometimes desirable to deliver the compounds of the present invention to the subject over prolonged periods of time, for example, for periods of one week to one year from a single administration. Various slow release, depot or implant dosage forms can be utilized. For example, a 15 dosage form can contain a pharmaceutically acceptable non-toxic salt of the compounds that has a low degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid such as phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a salt with a polyvalent metal cation such as zinc, calcium, bismuth, barium, magnesium, aluminum, 20 copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from e.g., N,N'-dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b) e.g. a zinc tannate salt. Additionally, the compounds of the present invention or, preferably, a relatively insoluble salt such as those just described, can be formulated in a gel, for example, an aluminum monostearate gel with, e.g. sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts, 25 pamoate salts, and the like. Another type of slow release depot formulation for injection would contain the compound or salt dispersed for encapsulated in a slow degrading, non-toxic, non-antigenic polymer such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. Pat. No. 3,773,919. The compounds or, preferably, relatively insoluble salts such as those described above can also be formulated in cholesterol matrix silastic pellets, particularly for use in animals. Additional slow 30 release, depot or implant formulations, e.g. gas or liquid liposomes are known in the literature (U.S. Pat. Nos. 5,770,222 and "Sustained and Controlled Release Drug Delivery Systems", J. R. Robinson ed., Marcel Dekker, Inc., N.Y., 1978).

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

**5 Example 1: Cloning and Expression of CNGH0004 polypeptide or antibody in Mammalian Cells**

A typical mammalian expression vector contains at least one promoter element, which mediates the initiation of transcription of mRNA, the polypeptide or antibody coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter). Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pRES1neo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clonetech Labs, Palo Alto, CA), pcDNA3.1 (+/-), pcDNA/Zeo (+/-) or pcDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 67109). Mammalian host cells that could be used include human Hela 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the gene can be expressed in stable cell lines that contain the gene integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded polypeptide or antibody, e.g., as a desired portion of at least one of SEQ ID NO:1. The DHFR (dihydrofolate reductase) marker is useful to develop cell lines that carry several hundred or even several thousand copies of the gene of interest. Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy, et al., Biochem. J. 227:277-279 (1991); Bebbington, et al., Bio/Technology 10:169-175 (1992)). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are used for the production of antibodies or polypeptides of the present invention.

The expression vectors pC1 and pC4 contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment of the CMV-enhancer (Boshart, et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors contain in addition the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene.

**5 Cloning and Expression in CHO Cells**

The vector pC4 is used for the expression of CNGH0004 antibody or polypeptide, e.g., using a coding sequence for at least one of SEQ ID NO:1, such as but not limited to SEQ ID NO:2. Plasmid pC4 is a derivative of the plasmid pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary- or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a selective medium (e.g., alpha minus MEM, Life Technologies, Gaithersburg, MD) supplemented with the chemotherapeutic agent methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented (see, e.g., F. W. Alt, et al., J. Biol. Chem. 253:1357-1370 (1978); J. L. Hamlin and C. Ma, Biochem. et Biophys. Acta 1097:107-143 (1990); and M. J. Page and M. A. Sydenham, Biotechnology 9:64-68 (1991)). Cells grown in increasing concentrations of MTX develop resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach can be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the methotrexate is withdrawn, cell lines are obtained that contain the amplified gene integrated into one or more chromosome(s) of the host cell.

Plasmid pC4 contains coding DNA for expressing the gene of interest under control of the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment isolated from the enhancer of the immediate early gene of human cytomegalovirus (CMV) (Boshart, et al., Cell 41:521-530 (1985)). Downstream of the promoter are BamHI, XbaI, and Asp718 restriction enzyme cleavage sites that allow integration of the genes. Behind these cloning sites the plasmid contains the 3' intron and polyadenylation site of the rat preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human b-actin promoter, the SV40 early or late promoters or the long terminal repeats from other retroviruses, e.g., HIV and HTLV. Clontech's Tet-Off and Tet-On gene expression systems and similar systems can be used to express the CNGH0004 polypeptide in a regulated way in mammalian cells (M. Gossen, and H. Bujard, Proc. Natl. Acad. Sci. USA 89: 5547-5551 (1992)). For the polyadenylation of the mRNA other signals, e.g., from the human growth hormone or globin genes can be used as well. Stable cell lines carrying a gene of interest integrated into the chromosomes can also be selected upon co-transfection with a selectable marker such as gpt, G418 or hygromycin. It can be advantageous to use more than one selectable marker in the beginning, e.g., G418 plus methotrexate.

The plasmid pC4 is digested with restriction enzymes and then dephosphorylated using calf

5 intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

The DNA sequence encoding the desired CNGH0004 antibody or polypeptide is used, e.g., DNA or RNA coding for at least one of SEQ ID NO:1, such as but not limited to SEQ ID NO:2 corresponding to at least one portion of at least one CNGH0004 antibody polypeptide of the present 10 invention, according to known method steps.

The isolated encoding DNA and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

Chinese hamster ovary (CHO) cells lacking an active DHFR gene are used for transfection. 5 15  $\mu$ g of the expression plasmid pC4 is cotransfected with 0.5  $\mu$ g of the plasmid pSV2-neo using lipofectin. The plasmid pSV2neo contains a dominant selectable marker, the neo gene from *Tn5* encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1  $\mu$ g/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 20 10, 25, or 50 ng/ml of methotrexate plus 1  $\mu$ g/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 mM, 2 mM, 5 mM, 10 mM, 20 mM). The same procedure is 25 repeated until clones are obtained that grow at a concentration of 100 - 200 mM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reverse phase HPLC analysis.

Example 2: Discovery of CNGH0004 nucleic acid and amino acid sequences and fragments and domains thereof

Skin biopsy samples were collected from patients with moderate to severe psoriasis. Seven samples were obtained at baseline (week 0) from lesional sites. Five were obtained from lesional site at 2 weeks post-infliximab treatment. Total RNA were extracted from each biopsy sample and were hybridized to two different types of cDNA arrays. RNA preparation, labeling, and hybridization were 30 performed as reported previously (9). Raw intensity data from the cDNA arrays were first normalized within each sample. Linear normalization and then nonlinear normalization was performed within each 35 sample. Outlier intensity data points (greater than 1.4 fold away from the median of replicate

5 measurements) were identified and removed from the data sets. The average intensity was generated by calculating the arithmetic mean of nonoutlier intensity values. Spline normalization of the average intensity was then performed across all samples in the data sets. Sample comparison was made between week 0 and week 2.

10 Data mining was performed using OmniViz software (Maynard, MA). Data comparisons were expressed as ratios in OmniViz and the log<sub>2</sub> of ratios were used to cluster expression data. Clustering was performed first using the Kmeans method. All genes were filtered by a single fold change greater than or equal to 2 for either increase or decrease in expression. Genes that past the filters were then clustered using a hierarchical method and correlation metric.

#### Description of CNGH0004 gene

15 CNGH0004 is located on Chromosome 9q31.3, from nucleotide 1065860007 to 106800277 on the minus strand based on the human reference sequence (UCSC version hg15, which is based on NCBI Build 33 and was produced by the International Human Genome Sequencing Consortium). The human genome sequence covers about 99 percent of the gene-containing regions in the genome, and has been sequenced to an accuracy of 99.99 percent. CNGH0004 neighbors MUSK gene at 5' end and TXN gene at 3' end. The gene is 214270 base pairs long, spreading over three BACs, AL592463, AL354982, and AL158158 from 5' to 3'.

20 Known mRNAs mapped to this region include Homo sapiens likely ortholog of mouse polydom (NM\_024500), Homo sapiens cDNA FLJ14964 fis(AK027870), Homo sapiens mRNA full length insert cDNA clone EUROIMAGE 248114 (AL079279), Homo sapiens serologically defined breast cancer antigen NY-BR-38 mRNA (AF308289), and Homo sapiens cDNA FLJ13529 fis (AK023591).

25 CNGH0004 transcript is 11,996 bp long. The transcript includes 5' UTR of 1000 bp, 48 exons, and 3' UTR of 280 bp. The ployA signal sequence is not identified.

30 Polymorphism analysis against public SNP database (<http://www.ncbi.nlm.nih.gov/SNP/>) as well as NM\_024500 revealed 12 SNPs within CNGH0004 coding region (CDS). Eight of the 12 changes result in non-synonymous changes at amino acid level (Table 1).

35 Conceptual translation of CNGH0004 results in a polypeptide of 3571 amino acid residues. It shares 81.7% residues with mouse Polydom (10) across the entire length and seems to be an ortholog of the mouse protein.

Both proteins share significant overall domain structures: an N-terminal signal peptide followed by a Von Willebrand factor (VWA) domain, 3 CCP (Sushi) domains, 2 Hyalin domains, 1 more CCP domain, 6 EGF-like domains, a Pentaxin domain, 2 more CCP domains, one EGF-like

5 domain, 28 more CCP domains, and 3 more EGF-like domains at the very C-terminus. There is another unclassified cystein-rich domain (pfam-B\_232) that repeated 4 times at the N-terminal portion of the protein (Table 2).

Sequence analysis shows that CNGH0004 and mouse Polydom represent a new sub-family within the EGF superfamily of protein. The members of this sub-family include Q9VM55 of 10 *Drosophila melanogaster*, and Q20535 of *C. elegans*. The common signature of this family is a combination of CCP, EGF-like and Hyalin domain, often repeated many times. Based on the distribution pattern of these domains in other proteins, CNGH0004 protein can be classified as a secreted extracellular matrix protein probably involves in tissue remodeling.

VWA domains in extracellular eukaryotic proteins mediate adhesion via metal ion-dependent 15 adhesion sites (MIDAS). It has been implicated in the immune and haemostatic systems, cell adhesion or matrix assembly (11).

CCP domain, also known as Sushi repeat or short complement-like repeat (SCR), is approximately 60 amino acid residues long and has been identified in most components and regulatory 20 proteins of the complement cascade. Prototype members of this protein family are molecules that regulate the complement system (12, 13). CCP repeats have also been identified in the selectin family of adhesion molecules. CCP modules contain proteins of the complement system (14).

Hyalin Repeat, also known as HYR domain, is named after the protein hyalin that is composed exclusively of this repeat. This domain probably corresponds to a new superfamily in the immunoglobulin fold. This domain may be involved in cell adhesion (15).

25 EGF-like (including EGF\_CA) domain is found in the sequence of epidermal growth factor (EGF) and in a large number of membrane-bound and extracellular proteins with various biological functions such as blood coagulation, control of cell fate, cell adhesion, activation of complement and fibrinolysis (16, 17). Many of these proteins require calcium for their biological function. A calcium-binding site has been found to be located at the N-terminus of the EGF-like domains. Calcium-binding 30 may be crucial for numerous protein-protein interactions.

Pentaxins (or pentraxins) are a family of proteins that show, under electron microscope, a discoid arrangement of five noncovalently bound subunits. Proteins of the pentraxin family are involved in acute immunological responses. PTX domain mediates binding of a variety of ligands which is Calcium-dependent (18).

35

#### Example 3: Expression of CNGH0004 in normal and diseased human tissues

We queried microarray expression database at Johnson & Johnson Pharmaceutical R&D at La

5 Jolla, as well as public expression database such as SAGE (<http://www.ncbi.nlm.nih.gov/SAGE/>). CNGH0004 gene is expressed at a high level in normal placenta and fetal tissues. It's at a lower, but detectable level in adult tissues including breast, ear, heart, pancreas, nose, and brain tissues.

We validated the above findings with real-time quantitative PCR using ABI Prism 7900 Sequence Detection System (Applied Biosystems; Foster City, CA). Human tissue master plate was 10 prepared according to Pinhasov et al (19). Total RNA from 83 representative human tissues was purchased from Strategene (La Jolla, CA).

Two primer-probe sets were ordered from Applied Biosystem as their Assays-on-Demand™ Gene Expression Products (Foster City, CA): Hs00225829\_m1, which covers sequence GGTGTGTGGAGCGCCACTGTTCCAC that correspond to 2475–2499 of CNGH0004; and 15 Hs00295944\_m1, which covers sequence ATGCAAAGAGACCAGGTGTGAAACT that corespond to 10879–10903 of CNGH0004. As shown in Table 3, both primer-probes sets yield similar results that are in agreement with *in silico* findings.

Expression of CNGH0004 in most human tissues is very low (table 3). Moderate expression can be detected in adrenal, colon, lung, ovary, pericardium, skin, spleen, stomach, testis, and thymus. 20 The highest expression by far is in placenta, which is at least over 20-fold increase compared to those tissues with moderate expression. CNGH0004 is virtually undetectable in the 10 cell lines we tested.

In certain cancer tissues, however, CNGH0004 expression is significantly elevated. These include glioblastoma, melanoma, colon epithelia, prostate carcinoma, ovary serous adenocarcinoma, pancreas neoplasia, and stomach adeno-carcinoma.

25 CNGH0004 is also detected at above-normal levels in asthmatic airway smooth muscle cells.

Expression level of CNGH0004 is lower in psoriatic lesional areas as compared to non-lesional areas. REMICADE treatment restores its level back to normal.

#### **Example 4: CNGH0004 involvement in cell migration and invasion of metastasis tumors**

The establishment of metastasis requires that tumor cells acquire new adhesion and migration properties to emigrate from primary sites and colonize distant organs. CNGH0004 is a cell membrane protein often overexpressed on tumor cells and, being both a cell-cell and cell-extracellular matrix adhesion protein, is well positioned to contribute to this process. Indeed, a fragment of CNGH0004 was identified as serologically defined breast cancer antigen NY-BR-38 mRNA. Furthermore, the interaction of CNGH0004 with other cellular proteins involved in motogenesis and proteolysis is a 30 determinant factor in cell migration and invasion.

35 The role of CNGH0004 in angiogenesis can also be investigated using *in vitro* cell migration

5 and invasion assays. Human microvascular endothelial cells (HMVEC) transfected with CNGH0004 gene, or its antisense, or siRNA constructs, are seeded in the top wells of the transwell system, in cell medium containing 1% FBS. In the bottom wells, culturing medium with 10% FBS serve as a chemotactic source to induce cell migration or invasion. The top and bottom wells are separated by a membrane with pores of 8  $\mu$ m in diameter. The membrane is either uncoated or coated with various 10 extracellular matrix proteins, i.e., collagen, fibronectin, vitronectin, or Matrigel, for determining cell migration or invasion. It is expected that modulation of CNGH0004 changes the properties of endothelial cell migration and invasion stimulation. The specificity of CNGH0004 in endothelial cell migration and invasion are investigated using CNGH0004 antibody of the present invention. Such antibodies block at least one biological activity of CNGH0004.

15

#### Advantage/Utilities

CNGH0004 gene is a human ortholog of the mouse Polydom gene. After conceptual translation, the two proteins share extensive homology (81.7%) that is also reflected on their protein domain patterns. The extremely high evolutional conservation implied that the function of CNGH0004 20 and Polydom is essential to human and mouse, respectively. It is also evident from its ubiquitous expression pattern in embryonic tissues in human and mouse.

Based on N-terminal signal peptide, CNGH0004 protein is predicted to be an extracellular matrix protein. All CNGH0004 protein domains are characterized as extracellular domains.

With 10 EGF domains, which tend to be glycosylated, CNGH0004 is likely to be post-25 translationally modified (PTM), such as glycosylation. With its high molecular weight and the possible PTM, CNGH0004 is likely distributed in the vicinity of cells that express it. As a target, it is amendable for localized treatment such as subcutaneous injection. Since it is accessible for antagonists and agonists thereto including monoclonal antibodies, vaccines, and adjuvants, CNGH0004 can well be suited for an antibody target.

30 In addition to normal placenta and fetal tissue development, protein domains that constitute CNGH0004 are probably also involved in tissue remodeling of airway smooth muscle as well as psoriatic epithelium. Based on its domain structure, CNGH0004 may function through mediating adhesion via metal ion-dependent adhesion sites (MIDAS), or via modulating complement control related to immunological responses. As such, CNGH0004 is a potential therapeutic target for treatment 35 of autoimmune or chronic inflammatory diseases including, but not limited to psoriasis or asthma, and different types of cancers.

5 Table 1. Non-synonymous SNPs within CNGH0004

Nucleotide position	Nucleotide change	Amino acid position	Amino acid change
2286	C>T	429	Ser>Leu
2519	G>A	507	Val>Ile
3526	C>G	842	Cys>Trp
3939	A>G	980	Glu>Gly
4188	A>G	1063	Tyr>Cys
5246	A>C	1416	Lys>Gln
5325	A>T	1442	Asp>Val
6429	C>A	A1810E	Ala>Glu

Table 2. Protein domains and locations on CNGH0004.

10

Domain Name	Pfam ID	Start residue	End residue
Signal Peptide		1	41
VWA		83	259
Pfam-B_232		305	360
Sushi/CCP	PF00084	378	433
Sushi/CCP	PF00084	438	493
Sushi/CCP	PF00084	498	559
HYR	PF02494	561	642
HYR	PF02494	643	722
CCP	PF00084	727	787
Pfam-B_232		999	1036
Pfam-B_232		1041	1106
Pfam-B_232		1108	1160
EGF-like	PF00008	1196	1229
EGF-like	PF00008	1231	1267
EGF-like	PF00008	1269	1305
EGF-like	PF00008	1307	1343
EGF-like	PF00008	1345	1381

EGF-like	PF00008	1383	1419
Pentaxin		1431	1623
Sushi/CCP	PF00084	1631	1685
Sushi/CCP	PF00084	1690	1743
EGF-like	PF00008	1748	1784
Sushi/CCP	PF00084	1789	1842
Sushi/CCP	PF00084	1847	1900
Sushi/CCP	PF00084	1905	1958
Sushi/CCP	PF00084	1963	2016
Sushi/CCP	PF00084	2021	2078
Sushi/CCP	PF00084	2083	2141
Sushi/CCP	PF00084	2146	2199
Sushi/CCP	PF00084	2204	2259
Sushi/CCP	PF00084	2264	2318
Sushi/CCP	PF00084	2323	2376
Sushi/CCP	PF00084	2381	2435
Sushi/CCP	PF00084	2440	2493
Sushi/CCP	PF00084	2498	2551
Sushi/CCP	PF00084	2556	2608
Sushi/CCP	PF00084	2660	2712
Sushi/CCP	PF00084	2717	2770
Sushi/CCP	PF00084	2775	2828
Sushi/CCP	PF00084	2833	2886
Sushi/CCP	PF00084	2891	2944
Sushi/CCP	PF00084	2949	3002
Sushi/CCP	PF00084	3007	3059
Sushi/CCP	PF00084	3064	3117
Sushi/CCP	PF00084	3122	3176
Sushi/CCP	PF00084	3181	3236
Sushi/CCP	PF00084	3241	3294
Sushi/CCP	PF00084	3299	3352
Sushi/CCP	PF00084	3357	3411
Sushi/CCP	PF00084	3416	3463

EGF-like	PF00008	3468	3499
EGF-like	PF00008	3504	3531
EGF-like	PF00008	3536	3563

5 Table 3. Relative expression of CNGH0004 in 82 human tissues \*

Human RNA	Hs00295944	Hs00225829
Adrenal, Female, Adult	10.03	8.38
Aorta, Female, Fetal	1.00	1.00
Bladder, Male, Adult	6.77	5.27
Bladder, Diseased, Male, Adult	1.42	0.51
Bladder, Female, Fetal	11.07	9.16
Bladder, Male, Fetal	9.54	7.75
Brain, Female, Fetal	1.85	1.39
Brain, Male, Adult	2.38	1.79
Brain, Male, Fetal	0.87	0.95
Brain, Occipital Cortex, Male, Adult	2.78	2.43
Brain, Parietal Cortex, Male, Adult	2.08	2.05
Breast, Female, Adult	6.02	4.89
Caval Vein, Male, Adult	7.86	6.16
Cervix, Female, Adult	6.30	5.13
Colon, Female, Adult (Top)	57.59	54.30
Colon, Ascending, Female, Adult	7.68	5.97
Colon, Descending, Female, Adult	6.26	5.10
Colon, Normal, Male, Adult (Matched Set)	5.46	4.44
Colon, Diseased, Male, Adult (Matched Set)	5.48	4.62
Colon, Female, Fetal	9.62	7.86
Colon, Male, Adult	4.57	3.46
Colon, Male, Adult (Normal)	7.15	5.95
Colon, Male, Adult (Diseased)	4.98	4.13
Colon, Male, Fetal	8.78	6.81
Heart, Female, Adult	1.65	1.61
Heart, Female, Fetal	5.91	4.83
Heart, Left Atrium, Male, Adult	2.53	2.26
Heart, Male, Adult	3.59	3.26
Ileum, Diseased, Male, Adult	3.07	2.17
Ileum, Diseased, Male, Adult (Matched Set)	3.45	2.52
Ileum, Diseased, Male, Adult (Matched Set)	2.88	1.86
Kidney, Female, Fetal	4.42	3.28
Kidney, Diseased, Female, Adult (Matched Set)	8.34	6.60
Kidney, Diseased, Female, Adult (Matched Set)	3.91	3.60
Kidney, Female, Adult	7.48	5.65
Kidney, Male, Adult	1.28	0.98
Kidney, Male, Fetal	7.10	5.89
Larynx, Diseased, Male, Adult (Matched Set)	4.74	3.67
Larynx, Diseased, Male, Adult (Matched Set)	2.66	0.91
Larynx, Male, Adult	5.52	4.38
Larynx, Male, Adult	2.84	0.92
Larynx, Male, Adult (Normal)	9.50	7.67
Liver, Female, Adult	0.91	0.61
Liver, Female, Fetal	1.44	1.19
Liver, Male, Adult	3.75	3.03

Liver, Male, Fetal	1.69	1.36
Lung, Female, Adult	17.53	14.73
Lung, Female, Fetal	3.14	3.04
Lung, Male, Adult	11.47	9.77
Lung, Male, Fetal	8.69	7.67
Lymph Node, Male, Adult	2.33	1.79
Ovary, Female, Adult	23.13	17.83
Pancreas, Male, Adult	3.58	3.34
Parotid, Female, Adult	0.86	0.70
Penis, Male, Adult	8.64	6.83
Pericardium, Male, Adult	20.82	17.52
Placenta, Adult, Female	301.40	312.48
Prostate, Male, Adult	0.70	0.49
Rectum, Male, Adult	4.45	3.24
Skeletal Muscle, Female, Fetal	9.23	7.83
Skeletal Muscle, Male, Adult	6.32	5.32
Skeletal Muscle, Male, Fetal	9.57	8.85
Skin, Female, Adult	4.58	3.77
Skin, Female, Fetal	16.90	14.71
Skin, Male, Adult	28.13	23.60
Spleen, Female, Adult	5.82	4.61
Spleen, Female/Male pooled, Fetal	20.46	18.03
Spleen, Male, Adult	8.03	6.06
Stomach, Diseased, Female, Adult (Matched Set)	4.42	3.58
Stomach, Diseased, Female, Adult (Matched Set)	7.31	5.46
Stomach, Female, Adult	1.76	1.59
Stomach, Female, Fetal	13.89	10.74
Stomach, Male, Adult	3.12	2.12
Stomach, Male, Fetal	10.54	8.70
Testes, Male, Adult	14.52	12.14
Thymus, Male and Female, Fetal	1.21	0.89
Thymus, Male, Adult	15.42	12.14
Thyroid, Female, Adult	5.45	4.17
Tongue, Male/Female, Adult	7.27	5.91
Trachea, Female, Adult	5.90	4.60
Uterus, Female, Adult	7.94	5.72
Vulva, Diseased, Female, Adult	1.51	0.71

5

\* Relative expression is calculated using a formula according to manufacturer's instruction (User Bulletin #2: ABI PRISM 7700 Sequence Detection System, Applied Biosystems, Foster City, CA). Evaluation of the copy number of mRNA of our gene of interest, CNGH0004, in specific tissues examined as shown in the table was compared with that of a calibrator tissue, in this case, Female Fetal

5 It will be clear that the invention can be practiced otherwise than as particularly described in the foregoing description and examples.

Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

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## 5 WHAT IS CLAIMED IS:

1. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide comprising or complementary to the all of the contiguous nucleic acids 1001-11713 of SEQ ID NO:1.
2. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide comprising or complementary to at least 45 contiguous nucleotides 1001-11713 of SEQ ID NO:1.
3. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide encoding the amino acid sequence of SEQ ID NO:2, or a polynucleotide complementary thereto.
4. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide having at least 95-99% identity to a nucleotide sequence comprising or complementary to all of the contiguous nucleotides 1001-11713 of SEQ ID NO:1.
5. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide having at least 95-99% identity to a nucleotide sequence comprising or complementary to at least 45 of the contiguous nucleotides 1001-11713 of SEQ ID NO:1.
6. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide that hybridizes under stringent conditions to all of the contiguous nucleotides of SEQ ID NO:1 or a polynucleotide complementary thereto.
7. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide that hybridizes under stringent conditions to at least 45 contiguous nucleotides of SEQ ID NO:1 or a polynucleotide complementary thereto.
8. At least one CNGH0004 polypeptide, comprising all of the contiguous amino acids of SEQ ID NO:2.
9. At least one CNGH0004 polypeptide, comprising at least 15 contiguous amino acids of SEQ ID NO:2.
10. At least one CNGH0004 polypeptide, comprising at least one domain of SEQ ID NO:2.
11. At least one CNGH0004 polypeptide, comprising at least one polypeptide having at least 90-99% identity to an amino acid sequence comprising all of the contiguous amino acids of SEQ ID NO:2.
12. At least one CNGH0004 polypeptide, comprising at least one polypeptide having at least 90-99% identity to an amino acid sequence comprising at least 15 of the

5 contiguous amino acids of SEQ ID NO:2.

13. At least one CNGH0004 polypeptide, comprising at least one polypeptide encoded by at least one polynucleotide that hybridizes under stringent conditions to all of the contiguous nucleotides SEQ ID NO:1 or a polynucleotide complementary thereto.

14. At least one CNGH0004 polypeptide, comprising at least one polypeptide encoded by at least one polynucleotide that hybridizes under stringent conditions to at least 45 of the contiguous nucleotides SEQ ID NO:1 or a polynucleotide complementary thereto.

15. At least one CNGH0004 polypeptide, comprising at least one of 1-82, 83-259, 259-377, 378-433, 434-438, 438-493, 498-559, 1631-1685, 1690-1743, 1789-1842, 2021-2078, 2083-2141, 2146-2199, 2204-2259, 2264-2318, 2323-2376, 2381-2435, 2440-2493, 2498-2551, 2556-2608, 2660-2712, 2717-2770, 2775-2828, 2833-2886, 2891-2944, 2949-3002, 3007-3059, 3064-3117, 3122-3176, 3181-3236, 3241-3294, 3299-3352, 3357-3411, 3416-3468, 1231-1267, 1269-1305, 1307-1343, 1345-1381, 1383-1419, 1748-1784, 3468-3499, 3504-3531, 3536-3563, 1431-1623, 643-722, 561-642, 1196-1229, 727-787, 1847-1900, 1963-2016, 1905-1958, 999-1036, 1041-1106, 1108-1160, 1-41, or 305-360 of SEQ ID NO:1.

20. 16. A CNGH0004 nucleic acid or CNGH0004 polypeptide according to any of claims 1-15, wherein said polypeptide has at least one activity of at least one CNGH0004 polypeptide.

25. 17. A CNGH0004 antibody, comprising a monoclonal or polyclonal antibody, fusion protein, or fragment thereof, that specifically binds at least one CNGH0004 polypeptide according to any of claims 1-15.

18. A CNGH0004 nucleic acid encoding at least one CNGH0004 polypeptide or CNGH0004 antibody according to any of claim 1-17.

19. 20. A CNGH0004 vector comprising at least one isolated nucleic acid according to any of claims 1-7.

30. 20. A CNGH0004 host cell comprising an isolated nucleic acid according to claim 18.

21. A CNGH0004 host cell according to claim 20, wherein said host cell is at least one selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, Hep G2, 653, SP2/0, 293, NSO, DG44 CHO, CHO K1, HeLa, myeloma, or lymphoma cells, or any derivative, immortalized or transformed cell thereof.

22. A method for producing at least one CNGH0004 polypeptide or CNGH0004 antibody, comprising translating a nucleic acid according to claim 18 under conditions in

5 *vitro*, *in vivo* or *in situ*, such that the CNGH0004 polypeptide is expressed in detectable or recoverable amounts.

23. A composition comprising at least one CNGH0004 nucleic acid, CNGH0004 polypeptide, or CNGH0004 antibody according to any of claims 1-17.

10 24. A composition according to claim 23, wherein said composition further comprises at least one pharmaceutically acceptable carrier or diluent.

15 25. A composition according to claim 23, further comprising at least one composition comprising an therapeutically effective amount of at least one compound, composition or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

20 26. A composition according to claim 23, in a form of at least one selected from a liquid, gas, or dry, solution, mixture, suspension, emulsion or colloid, a lyophilized preparation, a powder.

27. A method for diagnosing or treating a CNGH0004 related condition in a cell, tissue, organ or animal, comprising

25 (a) contacting or administering a composition comprising an effective amount of at least one CNGH0004 nucleic acid, polypeptide or antibody according to any of claims 1-17, with, or to, said cell, tissue, organ or animal.

30 28. A method according to claim 27, wherein said effective amount is 0.001-50 mg of CNGH0004 antibody; 0.000001-500 mg of said CNGH0004 polypeptide; or 0.0001-100 $\mu$ g of said CNGH0004 nucleic acid per kilogram of said cells, tissue, organ or animal.

35 29. A method according to claim 27, wherein said contacting or said administrating is by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intraceelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

5                   30.         A method according to claim 27, further comprising administering, prior, concurrently or after said (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a  
10                  gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

15                  31.         A device, comprising at least one isolated CNGH0004 polypeptide, antibody or nucleic acid according to any of claims 1-17, wherein said device is suitable for contacting or administering said at least one of said CNGH0004 polypeptide, antibody or nucleic acid, by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, 20                  intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

25                  32.         An article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising at least one isolated CNGH0004 polypeptide, antibody or nucleic acid according to any of claims 1-17.

30                  33.         The article of manufacture of claim 32, wherein said container is a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitory, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

35                  34.         A method for producing at least one isolated CNGH0004 polypeptide, antibody or nucleic acid according to any of claims 1-17, comprising providing at least one host cell, transgenic animal, transgenic plant, plant cell capable of expressing in detectable or recoverable amounts said polypeptide, antibody or nucleic acid.

- 5            35.        At least one CNGH0004 polypeptide, antibody or nucleic acid,  
produced by a method according to claim 34.

## 5 SEQUENCE LISTING

&lt;110&gt; Huang, Chris.

Song, Xiao-yu

&lt;120&gt; CNGH0004 POLYPEPTIDES, ANTIBODIES,

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&lt;160&gt; 2

&lt;170&gt; PatentIn version 3.1

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&lt;211&gt; 11996

15 &lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1001)..(11716)

20 &lt;223&gt;

&lt;400&gt; 1

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aatgcacgac	tgaagtacca	tgacaaaatca	ttcctgtgg	acgcataagg	ttagatgcac	180			
25 ctcctttatg	gtgtgatctg	agggggccct	taagggctt	atctgcacgc	tcacacacac	240			
cactgattag	aatccccat	cagggaaaatt	gtacaatcat	ctatggcg	agggctttgg	300			
gacactgaat	ggggggaaaag	aaacacaaaa	ggtgagcag	cagtttcaa	aggatgtttt	360			
caactccctg	gcgcgtccgc	gtgtatgttt	tctctacaa	agttttcaa	attactgtgg	420			
cactctgg	atctggatcc	atctccatgt	attctctgt	cagctctgtc	cagacatatg	480			
30 ggatcaatca	gggccttcgc	gttggtgcgc	ttgtgtcggt	aatgttgaca	gcctgacaga	540			
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gagagggaga	gaaggaggaga	agcggggat	ttttttgtac	tggcccccctt	ccttcaaaca	720			
35 ttttataggc	tccagggaga	gagaggaggaga	ggagagagg	aagaaaaaaaaa	gaggagagcg	780			
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tttgtgtctgt	ccccatgtc	agatgaaagg	gctgtgagc	tcttggccgc	tgccccccgc	900			
40 45	ccagctccgc	gcacgcgcct	ctgcgatcc	ggccgcggccag	cgcccttcc	cgcccgagcc			
ccgcgcgtcg	ctccggggca	gcgcgtctgt	ctccagegcg	atg	tgg	cct	cgc	ctg	1015
				Met	Trp	Pro	Arg	Leu	
				1	5				

gcc	ttt	tgt	tgc	tgg	ggt	ctg	gcg	ctc	gtt	tcg	ggc	tgg	gcg	acc	ttt	1063	
Ala		Phe	Cys	Cys	Trp	Gly	Leu	Ala	Leu	Val	Ser	Gly	Trp	Ala	Thr	Phe	

10	15	20
----	----	----

cag	cag	atg	tcc	ccg	tgc	cgc	aat	ttc	agc	ttc	cgc	ctc	tcc	ccc	gag	1111
Gln	Gln	Met	Ser	Pro	Ser	Arg	Asn	Phe	Ser	Phe	Arg	Leu	Phe	Pro	Glu	

25	30	35
----	----	----

acc	gcg	ccc	ggg	gcc	ccc	ggg	agt	atc	ccc	gcg	ccg	ccc	gtt	ect	gga	1159
Thr	Ala	Pro	Gly	Ala	Pro	Gly	Ser	Ile	Pro	Ala	Pro	Pro	Ala	Pro	Gly	

40	45	50
----	----	----

5	gac gaa gcg gcg ggg age aga gtg gag cgg ctg ggc cag gcg ttc cgg	1207
	Asp Glu Ala Ala Gly Ser Arg Val Glu Arg Leu Gly Gln Ala Phe Arg	
55	55 60 65	
	cga cgc gtg cgg ctg ctg cgg gag ctc age gag cgc ctg gag ctt gtc	1255
	Arg Arg Val Arg Leu Leu Arg Glu Leu Ser Glu Arg Leu Glu Leu Val	
10	70 75 80 85	
	ttc ctg gtg gat gat tcc age gtg ggc gaa gtc aac ttc cgc age	1303
	Phe Leu Val Asp Asp Ser Ser Ser Val Gly Glu Val Asn Phe Arg Ser	
	90 95 100	
15	gag ctc atg ttc gtc cgc aag ctg ctg tcc gac ttc ccc gtg gtg ccc	1351
	Glu Leu Met Phe Val Arg Lys Leu Leu Ser Asp Phe Pro Val Val Pro	
	105 110 115	
	acg gcc acg cgc gtg gcc atc gtg acc ttc tcc aag dac tac tgc	1399
	Thr Ala Thr Arg Val Ala Ile Val Thr Phe Ser Ser Lys Asn Tyr Val	
	120 125 130	
20	gtg ccc cgc gtc gat tac atc tcc acc cgc cgc ggc cag cac aag	1447
	Val Pro Arg Val Asp Tyr Ile Ser Thr Arg Arg Ala Arg Gln His Lys	
	135 140 145	
	tgc gcg ctg ctc ctc caa gag atc cct gcc atc tcc tac cga ggt ggc	1495
	Cys Ala Leu Leu Leu Gln Glu Ile Pro Ala Ile Ser Tyr Arg Gly Gly	
25	150 155 160 165	
	ggc acc tac acc aag ggc gcc ttc cag caa gcc gcg caa att ctt ctt	1543
	Gly Thr Tyr Thr Lys Gly Ala Phe Gln Gln Ala Ala Gln Ile Leu Leu	
	170 175 180	
30	cat gct aga gaa aac tca aca aaa gtt gta ttt ctc atc act gat gga	1591
	His Ala Arg Glu Asn Ser Thr Lys Val Val Phe Leu Ile Thr Asp Gly	
	185 190 195	
	tat tcc aat ggg gga gac cct aga cca att gca gcg tca ctg cga gat	1639
	Tyr Ser Asn Gly Gly Asp Pro Arg Pro Ile Ala Ala Ser Leu Arg Asp	
	200 205 210	
35	tca gga gtg gag atc ttc act ttt ggc ata tgg caa ggg aac att cga	1687
	Ser Gly Val Glu Ile Phe Thr Phe Gly Ile Trp Gln Gly Asn Ile Arg	
	215 220 225	
	gag ctg aat gac atg gct tcc acc cca aag gag gag cac tgt tac ctg	1735
	Glu Leu Asn Asp Met Ala Ser Thr Pro Lys Glu Glu His Cys Tyr Leu	
40	230 235 240 245	
	cta cac agt ttt gaa gaa ttt gag gct tta gct cgc cgg gca ttg cat	1783
	Leu His Ser Phe Glu Glu Phe Glu Ala Leu Ala Arg Arg Ala Leu His	
	250 255 260	
	gaa gat cta cct tct ggg agt ttt att caa gat gat atg gtc cac tgc	1831
45	Glu Asp Leu Pro Ser Gly Ser Phe Ile Gln Asp Asp Met Val His Cys	
	265 270 275	
	tca tat ctt tgt gat gaa ggc aag gac tgc tgt gac cga atg gga agc	1879
	Ser Tyr Leu Cys Asp Glu Gly Lys Asp Cys Cys Asp Arg Met Gly Ser	
	280 285 290	

5	tgc aaa tgt ggg aca cac aca ggc cat ttt gag tgc atc tgt gaa aag Cys Lys Eys Gly Thr His Thr Gly His Phe Glu Cys Ile Cys Glu Lys 295 300 305	1927
10	ggg tat tac ggg aaa ggt ctg cag tat gaa tgc aca gct tgc cca tcg Gly Tyr Tyr Gly Lys Gly Leu Gln Tyr Glu Cys Thr Ala Cys Pro Ser 310 315 320 325	1975
15	ggg aca tac aaa cct gaa ggc tca cca gga gga atc agc agt tgc att Gly Thr Tyr Lys Pro Glu Gly Ser Pro Gly Gly Ile Ser Ser Cys Ile 330 335 340	2023
20	cca tgt cct gat gaa aat cac acc tct cca cct gga agc aca tcc cct Pro Cys Pro Asp Glu Asn His Thr Ser Pro Pro Gly Ser Thr Ser Pro 345 350 355	2071
25	gaa gac tgt gtc tgc aga gag gga tac agg gca tct ggc cag acc tgt Glu Asp Cys Val Cys Arg Glu Gly Tyr Arg Ala Ser Gly Gln Thr Cys 360 365 370	2119
30	gaa ctt gtc cac tgc cct gcc ctg aag cct ccc gaa aat ggt tac ttt Glu Leu Val His Cys Pro Ala Leu Lys Pro Pro Glu Asn Gly Tyr Phe 375 380 385	2167
35	atc caa aac act tgc aac aac cac ttc aat gca gcc tgt ggg gtc cga Ile Gln Asn Thr Cys Asn Asn His Phe Asn Ala Ala Cys Gly Val Arg 390 395 400 405	2215
40	tgt cac cct gga ttt gat ctt gtg gga agc agc atc atc tta tgt cta Cys His Pro Gly Phe Asp Leu Val Gly Ser Ser Ile Ile Leu Cys Leu 410 415 420	2263
45	ccc aat ggt ttg tgg tcc ggt tca gag agc tac tgc aga gta aga aca Pro Asn Gly Leu Trp Ser Gly Ser Glu Ser Tyr Cys Arg Val Arg Thr 425 430 435	2311
50	tgt cct cat ctc cgc cag ccg aaa cat ggc cac atc agc tgt tct aca Cys Pro His Leu Arg Gln Pro Lys His Gly His Ile Ser Cys Ser Thr 440 445 450	2359
55	agg gaa atg tta tat aag aca aca tgc ttg gtt gcc tgt gat gaa ggg Arg Glu Met Leu Tyr Lys Thr Thr Cys Leu Val Ala Cys Asp Glu Gly 455 460 465	2407
60	tac aga cta gaa ggc agt gat aag ctt act tgt caa gga aac agc cag Tyr Arg Leu Glu Gly Ser Asp Lys Leu Thr Cys Gln Gly Asn Ser Gln 470 475 480 485	2455
65	tgg gat ggg cca gaa ccc cgg tgt gtg gag cgc cac tgt tcc acc ttt Trp Asp Gly Pro Glu Pro Arg Cys Val Glu Arg His Cys Ser Thr Phe 490 495 500	2503
70	cag atg ccc aaa gat gtc atc ata tcc ccc cac aac tgt ggc aag cag Gln Met Pro Lys Asp Val Ile Ile Ser Pro His Asn Cys Gly Lys Gln 505 510 515	2551
75	cca gcc aaa ttt ggg acg atc tgc tat gta agt tgc cgc caa ggg ttc Pro Ala Lys Phe Gly Thr Ile Cys Tyr Val Ser Cys Arg Gln Gly Phe 520 525 530	2599

5	att tta tct gga gtc aaa gaa atg ctg aga tgt acc act tct gga aaa Ile Leu Ser Gly Val Lys Glu Met Leu Arg Cys Thr Thr Ser Gly Lys 535 540 545	2647
	tgg aat gtc gga gtt cag gca gct gtg tgt aaa gac gtg gag gct cct Trp Asn Val Gly Val Gln Ala Ala Val Cys Lys Asp Val Glu Ala Pro	2695
10	550 555 560 565 caa atc aac tgt cct aag gac ata gag gct aag act ctg gaa cag caa Gln Ile Asn Cys Pro Lys Asp Ile Glu Ala Lys Thr Leu Glu Gln Gln 570 575 580	2743
	gat tct gcc aat gtt acc tgg cag att cca aca gct aaa gac aac tct Asp Ser Ala Asn Val Thr Trp Gln Ile Pro Thr Ala Lys Asp Asn Ser 585 590 595	2791
15	99t gaa aag gtg tca gtc cac gtt cat cca get ttc acc cca cct tac Gly Glu Lys Val Ser Val His Val His Pro Ala Phe Thr Pro Pro Tyr 600 605 610	2839
	ctt ttc cca att gga gat gtt gct atc gta tac acg gca act gac cta Leu Phe Pro Ile Gly Asp Val Ala Ile Val Tyr Thr Ala Thr Asp Leu 615 620 625	2887
	tcc ggc aac cag gcc agc tgc att ttc cat atc aag gtt att gat gca Ser Gly Asn Gln Ala Ser Cys Ile Phe His Ile Lys Val Ile Asp Ala 630 635 640 645	2935
20	gaa cca cct gtc ata gac tgg tgc aga tct cca cct ccc gtc cag gtc Glu Pro Pro Val Ile Asp Trp Cys Arg Ser Pro Pro Pro Val Gln Val 650 655 660	2983
	tcg gag aag gta cat gcc gca agc tgg gat gag cct cag ttc tca gac Ser Glu Lys Val His Ala Ala Ser Trp Asp Glu Pro Gln Phe Ser Asp 665 670 675	3031
	aac tca ggg gct gaa ttg gtc att acc aga agt cat aca caa gga gac Asn Ser Gly Ala Glu Leu Val Ile Thr Arg Ser His Thr Gln Gly Asp 680 685 690	3079
25	ctt ttc cct caa ggg gag act ata gta cag tat aca gce act gac ccc Leu Phe Pro Gln Gly Glu Thr Ile Val Gln Tyr Thr Ala Thr Asp Pro 695 700 705	3127
	tca ggc aat aac agg aca tgt gat atc cat att gtc ata aaa ggt tct Ser Gly Asn Asn Arg Thr Cys Asp Ile His Ile Val Ile Lys Gly Ser 710 715 720 725	3175
30	ccc tgt gaa att cca ttc aca cct gta aat ggg gat ttt ata tgc act Pro Cys Glu Ile Pro Phe Thr Pro Val Asn Gly Asp Phe Ile Cys Thr 730 735 740	3223
	cca gat aat act gga gtc aac tgt aca tta act tgc ttg gag ggc tat Pro Asp Asn Thr Gly Val Asn Cys Thr Leu Thr Cys Leu Glu Gly Tyr 745 750 755	3271
35	gat ttc aca gaa ggg tct act gac aag tat tat tgt gct tat gaa gat Asp Phe Thr Glu Gly Ser Thr Asp Lys Tyr Tyr Cys Ala Tyr Glu Asp 760 765 770	3319

5 ggc gtc tgg aaa cca aca tat acc act gaa tgg cca gac tgt gcc aaa 3367  
 Gly Val Trp Lys Pro Thr Tyr Thr Thr Glu Trp Pro Asp Cys Ala Lys  
 775 780 785  
 aaa cgt ttt gca aac cac ggg ttc aag tcc ttt gag atg atc ttc tac aaa 3415  
 Lys Arg Phe Ala Asn His Gly Phe Lys Ser Phe Glu Met Phe Tyr Lys  
 10 790 795 800 805  
 gca gct cgt tgt gat gac aca gat ctg atg aag aag ttt tct gaa gca 3463  
 Ala Ala Arg Cys Asp Asp Thr Asp Leu Met Lys Lys Phe Ser Glu Ala  
 810 815 820  
 ttt gag acg acc ctg gga aaa atg gtc cca tca ttt tgt agt gat gca 3511  
 15 Phe Glu Thr Thr Leu Gly Lys Met Val Pro Ser Phe Cys Ser Asp Ala  
 825 830 835  
 gag gac att gac tgc aga ctg gag gag aac ctg acc aaa aaa tat tgc 3559  
 Glu Asp Ile Asp Cys Arg Leu Glu Glu Asn Leu Thr Lys Lys Tyr Cys  
 840 845 850  
 20 cta gaa tat aat tat gac tat gaa aat ggc ttt gca att gga cca ggt 3607  
 Leu Glu Tyr Asn Tyr Asp Tyr Glu Asn Gly Phe Ala Ile Gly Pro Gly  
 855 860 865  
 ggc tgg ggt gca gct aat agg ctg gat tac tct tac gat gac ttc ctg 3655  
 Gly Trp Gly Ala Ala Asn Arg Leu Asp Tyr Ser Tyr Asp Asp Phe Leu  
 25 870 875 880 885  
 gac act gtg caa gaa aca gcc aca aac atc ggc aat gcc aag tcc tca 3703  
 Asp Thr Val Gln Glu Thr Ala Thr Ser Ile Gly Asn Ala Lys Ser Ser  
 890 895 900  
 cggtt aat aaa aga agt gec cca tta tct gac tat aaa att aag tta att 3751  
 30 Arg Ile Lys Arg Ser Ala Pro Leu Ser Asp Tyr Lys Ile Lys Leu Ile  
 905 910 915  
 ttt aac atc aca gct agt gtg cca tta ccc gat gaa aga aat gat acc 3799  
 Phe Asn Ile Thr Ala Ser Val Pro Leu Pro Asp Glu Arg Asn Asp Thr  
 920 925 930  
 35 ctt gaa tgg gaa aat cag caa ega ctc ctt cag aca ttg gaa act atc 3847  
 Leu Glu Trp Glu Asn Gln Gln Arg Leu Leu Gln Thr Leu Glu Thr Ile  
 935 940 945  
 aca aat aaa ctg aaa agg act ctc aac aaa gac ccc atg tat tcc ttt 3895  
 Thr Asn Lys Leu Lys Arg Thr Leu Asn Lys Asp Pro Met Tyr Ser Phe  
 40 950 955 960 965  
 cag ctt gca tca gaa ata ctt ata gcc gac aca aat tca tta gaa aca 3943  
 Gln Leu Ala Ser Glu Ile Leu Ile Ala Asp Ser Asn Ser Leu Glu Thr  
 970 975 980  
 aaa aag gct tcc ccc ttc tgc aga cca ggc tca gtg ctg aga ggg cgt 3991  
 45 Lys Lys Ala Ser Pro Phe Cys Arg Pro Gly Ser Val Leu Arg Gly Arg  
 985 990 995  
 atg tgt gtc aat tgc cct ttg gga acc tat tat aat ctg gaa cat 4036  
 Met Cys Val Asn Cys Pro Leu Gly Thr Tyr Tyr Asn Leu Glu His  
 1000 1005 1010

5	tcc acc tgt gaa agc tgc egg atc gga tcc tat caa gat gaa gaa Phe Thr Cys Glu Ser Cys Arg Ile Gly Ser Tyr Gln Asp Glu Glu 1015 1020 1025	4081
	ggg caa ctt gag tgc aag ctt tgc ccc tct ggg atg tae acg gaa Gly Gln Leu Glu Cys Lys Leu Cys Pro Ser Gly Met Tyr Thr Glu 10 1030 1035 1040	4126
	tat atc cat tca aga aac atc tct gat tgt aat get cag tgt aaa Tyr Ile His Ser Arg Asn Ile Ser Asp Cys Lys Ala Gln Cys Lys 1045 1050 1055	4171
	caa ggc acc tac tca tac agt gga ctt gag act tgt gaa tcg tgt 15 Gln Gly Thr Tyr Ser Tyr Ser Gly Leu Glu Thr Cys Glu Ser Cys 1060 1065 1070	4216
	cca ctg ggc act tat cag cca aaa ttt ggt tcc cgg age tcg ctc Pro Leu Gly Thr Tyr Gln Pro Lys Phe Gly Ser Arg Ser Cys Leu 1075 1080 1085	4261
20	tgc tgt cca gaa aac acc tca act gtg aaa aga gga gcc gtg aac Ser Cys Pro Glu Asn Thr Ser Thr Val Lys Arg Gly Ala Val Asn 1090 1095 1100	4306
	att tct gca tgt gga gtt cct tgt cca gaa gga aaa ttc tcg cgt Ile Ser Ala Cys Gly Val Pro Cys Pro Glu Gly Lys Phe Ser Arg 25 1105 1110 1115	4351
	tct ggg tta atg ccc tgt eac cca tgt cct cgt gac tat tac caa Ser Gly Leu Met Pro Cys His Pro Cys Pro Arg Asp Tyr Tyr Gln 1120 1125 1130	4396
30	cct aat gca ggg aag gcc ttc tgc ctg gcc tgt ccc ttt tat gga Pro Asn Ala Gly Lys Ala Phe Cys Leu Ala Cys Pro Phe Tyr Gly 1135 1140 1145	4441
	act acc cca ttc gct ggt tcc aga tcc atc aca gaa tgt tca agt Thr Thr Pro Phe Ala Gly Ser Arg Ser Ile Thr Glu Cys Ser Ser 1150 1155 1160	4486
35	ttt agt tca act ttc tca gcg gca gag gaa agt gtg gtg ccc cct Phe Ser Ser Thr Phe Ser Ala Ala Glu Glu Ser Val Val Pro Pro 1165 1170 1175	4531
	gcc tct ctt gga cat att aaa aag agg cat gaa atc agc agt cag Ala Ser Leu Gly His Ile Lys Lys Arg His Glu Ile Ser Ser Gln 40 1180 1185 1190	4576
	gtt ttc cat gaa tgc ttc ttt aac cct tgc cac aat agt gga acc Val Phe His Glu Cys Phe Phe Asn Pro Cys His Asn Ser Gly Thr 1195 1200 1205	4621
45	tgc cag caa ctt ggg cgt ggt tat gtt tgt ctc tgt cca ctt gga Cys Gln Gln Leu Gly Arg Gly Tyr Val Cys Leu Cys Pro Leu Gly 1210 1215 1220	4666
	tat aca ggc tta aag tgt gaa aca gac atc gat gag tgc agc cca Tyr Thr Gly Leu Lys Cys Glu Thr Asp Ile Asp Glu Cys Ser Pro 1225 1230 1235	4711

5 ctg cct tgc ctc aac aat gga gtt tgt aaa gac cta gtt ggg gaa 4756  
 Leu Pro Cys Leu Asn Asn Gly Val Cys Lys Asp Leu Val Gly Glu  
 1240 1245 1250  
 ttc att tgt gag tgc cca tca ggt tac aca ggt cag cgg tgt gaa 4801  
 Phe Ile Cys Glu Cys Pro Ser Gly Tyr Thr Gly Gln Arg Cys Glu  
 10 1255 1260 1265  
 gaa aat ata aat gag tgt agc tcc agt cct tgt tta aat aaa gga 4846  
 Glu Asn Ile Asn Glu Cys Ser Ser Ser Pro Cys Leu Asn Lys Gly  
 1270 1275 1280  
 atc tgt gtt gat ggt gtg gct ggc tat cgt tgc aca tgt gtg aaa 4891  
 15 Ile Cys Val Asp Gly Val Ala Gly Tyr Arg Cys Thr Cys Val Lys  
 1285 1290 1295  
 gga ttt gta ggc ctg cat tgt gaa aca gaa gtc aat gaa tgc cag 4936  
 Gly Phe Val Gly Leu His Cys Glu Thr Glu Val Asn Glu Cys Gln  
 1300 1305 1310  
 20 tca aac cca tgc tta aat aat gca gtc tgt gaa gac cag gtt ggg 4981  
 Ser Asn Pro Cys Leu Asn Asn Ala Val Cys Glu Asp Gln Val Gly  
 1315 1320 1325  
 gga ttc ttg tgc aaa tgc cca cct gga ttt ttg ggt acc cga tgt 5026  
 Gly Phe Leu Cys Lys Cys Pro Pro Gly Phe Leu Gly Thr Arg Cys  
 25 1330 1335 1340  
 gga aag aac gtc gat gag tgt ctc agt cag cca tgc aaa aat gga 5071  
 Gly Lys Asn Val Asp Glu Cys Leu Ser Gln Pro Cys Lys Asn Gly  
 1345 1350 1355  
 gct acc tgt aaa gac ggt gcc aat age ttc aga tgc ctg tgt gca 5116  
 30 Ala Thr Cys Lys Asp Gly Ala Asn Ser Phe Arg Cys Leu Cys Ala  
 1360 1365 1370  
 gct ggc ttc aca gga tca cac tgt gaa ttg aac atc aat gaa tgt 5161  
 Ala Gly Phe Thr Gly Ser His Cys Glu Leu Asn Ile Asn Glu Cys  
 1375 1380 1385  
 35 cag tct aat cca tgt aga aat cag gcc acc tgt gtg gat gaa tta 5206  
 Gln Ser Asn Pro Cys Arg Asn Gln Ala Thr Cys Val Asp Glu Leu  
 1390 1395 1400  
 aat tca tac agt tgt aaa tgt cag cca gga ttt tca ggc aaa agg 5251  
 Asn Ser Tyr Ser Cys Lys Cys Gln Pro Gly Phe Ser Gly Lys Arg  
 40 1405 1410 1415  
 tgt gaa aca gaa cag tct aca ggc ttt aac ctg gat ttt gaa gtt 5296  
 Cys Glu Thr Glu Gln Ser Thr Gly Phe Asn Leu Asp Phe Glu Val  
 1420 1425 1430  
 tct ggc atc tat gga tat gtc atg cta gat ggc atg ctc cca tct 5341  
 45 Ser Gly Ile Tyr Gly Tyr Val Met Leu Asp Gly Met Leu Pro Ser  
 1435 1440 1445  
 ctc cat gct cta acc tgt acc ttc tgg atg aaa tcc tct gac gac 5386  
 Leu His Ala Leu Thr Cys Thr Phe Trp Met Lys Ser Ser Asp Asp  
 1450 1455 1460

5	atg aac tat gga aca cca atc tcc tat gca gtt gat aac ggc agc Met Asn Tyr Gly Thr Pro Ile Ser Tyr Ala Val Asp Asn. Gly Ser 1465 1470 1475	5431
	gac aat acc ttg ctc ctg act gat tat aac ggc tgg gtt ctt tat Asp Asn Thr Leu Leu Leu Thr Asp Tyr Asn Gly Trp Val Leu Tyr	5476
10	1480 1485 1490	
	gtg aat ggc agg gaa aag ata aca aac tgt ccc tgg gtg aat gat Val Asn Gly Arg Glu Lys Ile Thr Asn Cys Pro Ser Val Asn Asp 1495 1500 1505	5521
15	gge aga tgg cat cat att gca atc act tgg aca agt ggc aat ggc Gly Arg Trp His His Ile Ala Ile Thr Trp Thr Ser Ala Asn Gly 1510 1515 1520	5566
	atc tgg aaa gtc tat atc gat ggg aaa tta tct gac ggt ggt gct Ile Trp Lys Val Tyr Ile Asp Gly Lys Leu Ser Asp Gly Gly Ala 1525 1530 1535	5611
20	ggc ctc tct gtt ggt ttg ccc ata cct ggt ggt ggt gcg tta gtt Gly Leu Ser Val Gly Leu Pro Ile Pro Gly Gly Gly Ala Leu Val 1540 1545 1550	5656
	ctg ggg caa gag caa gac aaa aaa gga gag gga ttc agc cca gct Leu Gly Gln Glu Gln Asp Lys Lys Gly Glu Gly Phe Ser Pro Ala 25 1555 1560 1565	5701
25	gag tct ttt gtg ggc tcc ata agc cag ctc aac ctc tgg gac tat Glu Ser Phe Val Gly Ser Ile Ser Gln Leu Asn Leu Trp Asp Tyr 1570 1575 1580	5746
	gtc ctg tct cca cag cag gtg aag tca ctg gct acc tcc tgc cca 30 Val Leu Ser Pro Gln Gln Val Lys Ser Leu Ala Thr Ser Cys Pro 1585 1590 1595	5791
	gag gaa ctc agt aaa gga aac gtg tta gca tgg cct gat ttc ttg Glu Glu Leu Ser Lys Gly Asn Val Leu Ala Trp Pro Asp Phe Leu 1600 1605 1610	5836
35	tca gga att gtg ggg aaa gtg aag atc gat tct aag agc ata ttt Ser Gly Ile Val Gly Lys Val Lys Ile Asp Ser Lys Ser Ile Phe 1615 1620 1625	5881
	tgt tct gat tgc cca cgc tta gga ggg tca gtg cct cat ctg aga Cys Ser Asp Cys Pro Arg Leu Gly Gly Ser Val Pro His Leu Arg	5926
40	act gca tct gaa gat tta aag cca ggt tcc aaa gtc aat ctg ttc Thr Ala Ser Glu Asp Leu Lys Pro Gly Ser Lys Val Asn Leu Phe 1630 1635 1640	5971
	1645 1650 1655	
45	tgt gat cca ggc ttc cag ctg gtc ggg aac cct gtg cag tac tgt Cys Asp Pro Gly Phe Gln Leu Val Gly Asn Pro Val Gln Tyr Cys 1660 1665 1670	6016
	ctg aat caa gga cag tgg aca caa cca ctt cct cac tgt gaa cgc Leu Asn Gln Gly Gln Trp Thr Gln Pro Leu Pro His Cys Glu Arg 1675 1680 1685	6061

5	att agc tgt ggg gtg cca cct cct ttg gag aat ggc ttc cat tca Ile Ser Cys Gly Val Pro Pro Pro Leu Glu Asn Gly Phe His Ser 1690 1695 1700	6106
	gcc gat gac ttc tat gct ggc agc aca gta acc tac cag tgc aac Ala Asp Asp Phe Tyr Ala Gly Ser Thr Val Thr Tyr Gln Cys Asn 1705 1710 1715	6151
10	aat ggc tac tat cta ttg ggt gac tca agg atg ttc tgt aca gat Asn Gly Tyr Tyr Leu Leu Gly Asp Ser Arg Met Phe Cys Thr Asp 1720 1725 1730	6196
15	aat ggg agc tgg aac ggc gtt tca cca tcc tgc ctt gat gtc gat Asn Gly Ser Trp Asn Gly Val Ser Pro Ser Cys Leu Asp Val Asp 1735 1740 1745	6241
	gag tgt gca gtt gga tca gat tgt agt gag cat gct tct tgc ctg Glu Cys Ala Val Gly Ser Asp Cys Ser Glu His Ala Ser Cys Leu 1750 1755 1760	6286
20	aac gta gat gga tcc tac ata tgt tca tgt gtc cca ccg tac aca Asn Val Asp Gly Ser Tyr Ile Cys Ser Cys Val Pro Pro Tyr Thr 1765 1770 1775	6331
	gga gat ggg aaa aac tgt gca gaa cct ata aaa tgt aag gct cca Gly Asp Gly Lys Asn Cys Ala Glu Pro Ile Lys Cys Lys Ala Pro 1780 1785 1790	6376
25	gga aat ccg gaa aat ggc cac tcc tca ggt gag att tat aca gta Gly Asn Pro Glu Asn Gly His Ser Ser Gly Glu Ile Tyr Thr Val 1795 1800 1805	6421
	ggg gcc gca gtc aca ttt tcg tgt cag gaa gga tac cag ttg atg Gly Ala Ala Val Thr Phe Ser Cys Gln Glu Gly Tyr Gln Leu Met 1810 1815 1820	6466
30	gga gta acc aaa atc aca tgt ttg gag tct gga gaa tgg aat cat Gly Val Thr Lys Ile Thr Cys Leu Glu Ser Gly Glu Trp Asn His 1825 1830 1835	6511
35	cta ata cca tat tgt aaa gct gtt tca tgt ggt aaa ccg gct att Leu Ile Pro Tyr Cys Lys Ala Val Ser Cys Gly Lys Pro Ala Ile 1840 1845 1850	6556
	cca gaa aat ggt tgc att gag gag tta gca ttt act ttt ggc agc Pro Glu Asn Gly Cys Ile Glu Glu Leu Ala Phe Thr Phe Gly Ser 1855 1860 1865	6601
40	aaa gtg aca tat agg tgt aat aaa gga tat act ctg gcc ggt gat Lys Val Thr Tyr Arg Cys Asn Lys Gly Tyr Thr Leu Ala Gly Asp 1870 1875 1880	6646
	aaa gaa tca tcc tgt ctt gct aac agt tct tgg agt cat tcc cct Lys Glu Ser Ser Cys Leu Ala Asn Ser Ser Trp Ser His Ser Pro 1885 1890 1895	6691
45	cct gtg tgt gaa cca gtg aag tgt tct agt ccg gaa aat ata aat Pro Val Cys Glu Pro Val Lys Cys Ser Ser Pro Glu Asn Ile Asn 1900 1905 1910	6736

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5	aat gga aaa tat att ttg agt ggg ctt acc tac ctt tct act gca Asn Gly Lys Tyr Ile Leu Ser Gly Leu Thr Tyr Leu Ser Thr Ala 1915 1920 1925	6781
	tca tat tca tgc gat aca gga tac agc tta cag ggc cct tcc att Ser Tyr Ser Cys Asp Thr Gly Tyr Ser Leu Gln Gly Pro Ser Ile 1930 1935 1940	6826
10	att gaa tgc acg gct tct ggc atc tgg gac aga gcg cca cct gcc Ile Glu Cys Thr Ala Ser Gly Ile Trp Asp Arg Ala Pro Pro Ala 1945 1950 1955	6871
	tgt cac ctc gtc ttc tgt gga gaa cca cct gcc atc aaa gat gct Cys His Leu Val Phe Cys Gly Glu Pro Pro Ala Ile Lys Asp Ala 1960 1965 1970	6916
15	gtc att acg ggg aat aac ttc act ttc agg aac acc gtc act tac Val Ile Thr Gly Asn Asn Phe Thr Phe Arg Asn Thr Val Thr Tyr 1975 1980 1985	6961
20	act tgc aaa gaa ggc tat act ctt gct ggt ctt gac acc att gaa Thr Cys Lys Glu Gly Tyr Thr Leu Ala Gly Leu Asp Thr Ile Glu 1990 1995 2000	7006
	tgc ctg gcc gac ggc aag tgg agt aga agt gac cag cag tgc ctg Cys Leu Ala Asp Gly Lys Trp Ser Arg Ser Asp Gln Gln Cys Leu 2005 2010 2015	7051
25	gct gtc tcc tgt gag cca ccc att gtg gac cac gcc tct cca Ala Val Ser Cys Asp Glu Pro Pro Ile Val Asp His Ala Ser Pro 2020 2025 2030	7096
	gag act gcc cat cgg ctc ttt gga gac att gca ttc tac tac tgc Glu Thr Ala His Arg Leu Phe Gly Asp Ile Ala Phe Tyr Tyr Cys 2035 2040 2045	7141
30	tct gat ggt tac agc cta gca gac aat tcc cag ctt ctc tgc aat Ser Asp Gly Tyr Ser Leu Ala Asp Asn Ser Gln Leu Leu Cys Asn 2050 2055 2060	7186
	gcc cag ggc aag tgg gta ccc cca gaa ggt caa gac atg ccc cgt Ala Gln Gly Lys Trp Val Pro Pro Glu Gly Gln Asp Met Pro Arg 2065 2070 2075	7231
35	tgt ata gct cat ttc tgt gaa aaa cct cca tcg gtt tcc tat agc Cys Ile Ala His Phe Cys Glu Lys Pro Pro Ser Val Ser Tyr Ser 2080 2085 2090	7276
	atc ttg gaa tct gtg agc aaa gca aaa ttt gca gtc ggc tca gtt Ile Leu Glu Ser Val Ser Lys Ala Lys Phe Ala Ala Gly Ser Val 2095 2100 2105	7321
40	gtg agc ttt aaa tgc atg gaa ggc ttt gta ctg aac acc tca gca Val Ser Phe Lys Cys Met Glu Gly Phe Val Leu Asn Thr Ser Ala 2110 2115 2120	7366
	aag att gaa tgt atg aga ggt ggg cag tgg aac cct tcc ccc atg Lys Ile Glu Cys Met Arg Gly Gln Trp Asn Pro Ser Pro Met 2125 2130 2135	7411

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5	tcc atc cag tgc atc cct gtg cgg tgc gga gag cca cca agc atc Ser Ile Gln Cys Ile Pro Val Arg Cys Gly Glu Pro Pro Ser Ile 2140 2145 2150	7456
10	atg aat ggc tat gca agt gga tca aac tac agt ttt gga gcc atg Met Asn Gly Tyr Ala Ser Gly Ser Asn Tyr Ser Phe Gly Ala Met 2155 2160 2165	7501
15	gtg gtc tac agc tgc aac aag ggg ttc tac atc aaa ggg gaa aag Val Ala Tyr Ser Cys Asn Lys Gly Phe Tyr Ile Lys Gly Glu Lys 2170 2175 2180	7546
20	aag agc acc tgc gaa gcc aca ggg cag tgg agt agt cct ata ccg Lys Ser Thr Cys Glu Ala Thr Gly Gln Trp Ser Ser Pro Ile Pro 2185 2190 2195	7591
25	acg tgc cac cgg gta tct tgt ggt gaa cca cct aag gtt gag aat Thr Cys His Pro Val Ser Cys Gly Glu Pro Pro Lys Val Glu Asn 2200 2205 2210	7636
30	ggc ttt ctg gag cat aca act ggc agg atc ttt gag agt gaa gtc Gly Phe Leu Glu His Thr Thr Gly Arg Ile Phe Glu Ser Glu Val 2215 2220 2225	7681
35	agg tat cag tgt aac ccg ggc tat aag tca gtc gga agt cct gta Arg Tyr Gln Cys Asn Pro Gly Tyr Lys Ser Val Gly Ser Pro Val 2230 2235 2240	7726
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45	atg tgt gtt cct ctc gac tgt gga aaa cct ccc ccg atc cag aat Met Cys Val Pro Leu Asp Cys Gly Lys Pro Pro Pro Ile Gln Asn 2260 2265 2270	7816
50	ggc ttc atg aaa gga gaa aac ttt gaa gta ggg tcc aag gtt cag Gly Phe Met Lys Gly Glu Asn Phe Glu Val Gly Ser Lys Val Gln 2275 2280 2285	7861
55	ttt ttc tgt aat gag ggt tat gag ctt gtt ggt gac agt ctc tgg Phe Phe Cys Asn Glu Gly Tyr Glu Leu Val Gly Asp Ser Ser Trp 2290 2295 2300	7906
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65	tgc atg cct gcc aag tgc cca gag cgg ccc ctc ttg gaa aac cag Cys Met Pro Ala Lys Eys Pro Glu Pro Pro Leu Leu Glu Asn Gln 2320 2325 2330	7996
70	cta gta tta aag gag ttg acc acc gag gta gga gtt gtc aca ttt Leu Val Leu Lys Glu Leu Thr Thr Glu Val Gly Val Val Thr Phe 2335 2340 2345	8041
75	tcc tgt aaa gaa ggg cat gtc ctg cca ggc ccc tct gtc ctg aaa Ser Cys Lys Glu Gly His Val Leu Gln Gly Pro Ser Val Leu Lys 2350 2355 2360	8086

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5	tgc ttg cca tcc cag caa tgg aat gac tct ttc cct gtt tgt aag Cys Leu Pro Ser Gln Gln Trp Asn Asp Ser Phe Pro Val Cys Lys 2365 2370 2375	8131
	att gtt ctt tgt acc cca cct ccc cta att tcc ttt ggt gtc ccc Ile Val Leu Cys Thr Pro Pro Pro Leu Ile Ser Phe Gly Val Pro 10 2380 2385 2390	8176
	att cct tct tct gct ctt cat ttt gga agt act gtc aag tat tct Ile Pro Ser Ser Ala Leu His Phe Gly Ser Thr Val Lys Tyr Ser 2395 2400 2405	8221
	tgt gta ggt ggg ttt ttc cta aga gga aat tct acc acc ctc tgc 15 Cys Val Gly Gly Phe Phe Leu Arg Gly Asn Ser Thr Thr Leu Cys 2410 2415 2420	8266
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	gtg caa ggc ctt gcc tat ctc agg aca gct ctc tat acc tgc aag Val Gln Gly Leu Ala Tyr Leu Ser Thr Ala Leu Tyr Thr Cys Lys 25 2455 2460 2465	8401
	cca ggc ttt gaa ttg gtg gga aat act acc acc ctt tgt gga gaa Pro Gly Phe Glu Leu Val Gly Asn Thr Thr Thr Leu Cys Gly Glu 2470 2475 2480	8446
	aat ggt cac tgg ctt gga gga aaa cca aca tgt aaa gcc att gag 30 Asn Gly His Trp Leu Gly Gly Lys Pro Thr Cys Lys Ala Ile Glu 2485 2490 2495	8491
	tgc ctg aaa ccc aag gag att ttg aat ggc aaa ttc tct tac acg Cys Leu Lys Pro Lys Glu Ile Leu Asn Gly Lys Phe Ser Tyr Thr 2500 2505 2510	8536
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	ttt cgg ctc gaa ggt ccc agt gcc ttg acc tgt tta gag aca ggt Phe Arg Leu Glu Gly Pro Ser Ala Leu Thr Cys Leu Glu Thr Gly 40 2530 2535 2540	8626
	gat tgg gat gta gat gcc cca tct tgc aat gcc atc cac tgt gat Asp Trp Asp Val Asp Ala Pro Ser Cys Asn Ala Ile His Cys Asp 2545 2550 2555	8671
	tcc cca caa ccc att gaa aat ggt ttt gta gaa ggt gca gat tac 45 Ser Pro Gln Pro Ile Glu Asn Gly Phe Val Glu Gly Ala Asp Tyr 2560 2565 2570	8716
	agg tat ggt gcc ata atc atc tac agt tgc ttc cct ggg ttt cag Ser Tyr Gly Ala Ile Ile Ile Tyr Ser Cys Phe Pro Gly Phe Gln 2575 2580 2585	8761

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15	cat ata gat ttt gga gac tgg act aaa ctc aaa gat gac cag gga His Ile Asp Phe Gly Asp Cys Thr Lys Leu Lys Asp Asp Gln Gly 2620 2625 2630	8896
20	tat ttt gag caa gaa gac gac atg atg gaa gtt cca tat gtg act Tyr Phe Glu Gln Glu Asp Asp Met Met Glu Val Pro Tyr Val Thr 2635 2640 2645	8941
25	cct cac ect ect tat cat ttg gga gca gtg gct aaa acc tgg gaa Pro His Pro Pro Tyr His Leu Gly Ala Val Ala Lys Thr Trp Glu 2650 2655 2660	8986
30	aat aca aag gag tct cct gct aca cat tca tca aac ttt ctg tat Asn Thr Lys Glu Ser Pro Ala Thr His Ser Ser Asn Phe Leu Tyr 2665 2670 2675	9031
35	ggg acc atg gtt tca tac acc tgg aat cca gga tat gaa ctt ctg Gly Thr Met Val Ser Tyr Thr Cys Asn Pro Gly Tyr Glu Leu Leu 2680 2685 2690	9076
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	cct gaa aat ggc ttt ttg cgt ttt aca gag act agc atg gga agt Pro Glu Asn Gly Phe Leu Arg Phe Thr Glu Thr Ser Met Gly Ser 2725 2730 2735	9211
	gct gtg cag tat agc tgg aaa cct gga cac att cta gca ggc tct Ala Val Gln Tyr Ser Cys Lys Pro Gly His Ile Leu Ala Gly Ser 2740 2745 2750	9256
	gac tta agg ctt tgg cta gag aat aga aag tgg agt ggt gcc tcc Asp Leu Arg Leu Cys Leu Glu Asn Arg Lys Trp Ser Gly Ala Ser 2755 2760 2765	9301
	cca cgc tgt gaa gcc att tca tgc aaa aag cca aat cca gtc atg Pro Arg Cys Glu Ala Ile Ser Cys Lys Lys Pro Asn Pro Val Met 2770 2775 2780	9346
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15	Thr Cys Asn Glu Gly Phe Leu Leu	Glu Gly Ala Arg Ser	Arg Val	
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	Cys Leu Ala Asn Gly Ser Trp Ser	Gly Ala Thr Pro Asp	Cys Val	
	2875	2880	2885	
20	cct gtc aga tgt gcc acc ccc cca	caa ctg gcc aat ggg	gtg acg	9706
	Pro Val Arg Cys Ala Thr Pro Pro	Gln Leu Ala Asn Gly	Val Thr	
	2890	2895	2900	
	gaa ggc ctg gac tat ggc ttc atg	aag gaa gta aca ttc	cac tgt	9751
	Glu Gly Leu Asp Tyr Gly Phe Met	Lys Glu Val Thr Phe	His Cys	
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	cac gag ggc tac atc ttg cac ggt	gct cca aaa ctc acc	tgt cag	9796
	His Glu Gly Tyr Ile Leu His Gly	Ala Pro Lys Leu Thr	Cys Gln	
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	tca gat ggc aac tgg gat gca gag	att cct ctc tgt aat	cca gtc	9841
30	Ser Asp Gly Asn Trp Asp Ala Glu	Ile Pro Leu Cys Lys	Pro Val	
	2935	2940	2945	
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	Asn Cys Gly Pro Pro Glu Asp Leu	Ala His Gly Phe Pro	Asn Gly	
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	Phe Ser Phe Ile His Gly Gly His	Ile Gln Tyr Gln Cys	Phe Pro	
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	Gly Tyr Lys Leu His Gly Asn Ser	Ser Arg Arg Cys Leu	Ser Asn	
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	Gly Ser Trp Ser Gly Ser Ser Pro	Ser Cys Leu Pro Cys	Arg Cys	
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45	Ser Thr Pro Val Ile Glu Tyr Gly	Thr Val Asn Gly Thr	Asp Phe	
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	gac tgt gga aag gca gcc cgg att	cag tgc ttc aaa ggc	ttc aag	10111
	Asp Cys Gly Lys Ala Ala Arg Ile	Gln Cys Phe Lys Gly	Phe Lys	
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	Leu Leu Gly	Leu Ser Glu Ile Thr	Cys Glu Ala Asp Gly	Gln Trp	
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	Ser Ser Gly	Phe Pro His Cys Glu	His Thr Ser Cys Gly	Ser Leu	
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	Pro Met Ile	Pro Asn Ala Phe Ile	Ser Glu Thr Ser Ser	Trp Lys	
	3070	3075	3080		
	gaa aat gtg	ata act tac agc tgc	agg tct gga tat gtc	ata caa	10291
15	Glü Asn Val	Ile Thr Tyr Ser Cys	Arg Ser Gly Tyr Val	Ile Gln	
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	ggc agt tca	gat ctg att tgt aca	gag aaa ggg gta tgg	agc cag	10336
	Gly Ser Ser	Asp Leu Ile Cys Thr	Glu Lys Gly Val Trp	Ser Gln	
	3100	3105	3110		
20	ctt tat cca	gtc tgt gag ccc ttg	tcc tgt ggg tcc cca	ccg tct	10381
	Pro Tyr Pro	Val Cys Glu Pro Leu	Ser Cys Gly Ser Pro	Pro Ser	
	3115	3120	3125		
	gtc gce aat	gca gtg gca act gga	gag gca cac acc tat	gaa agt	10426
	Val Ala Asn	Ala Val Ala Thr Gly	Glu Ala His Thr Tyr	Glu Ser	
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	Glu Val Lys	Leu Arg Cys Leu Glu	Gly Tyr Thr Met Asp	Thr Asp	
	3145	3150	3155		
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	Arg Ile Ser	Cys Ser Pro Lys Lys	Cys Pro Leu Pro Glu	Asn Ile	
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	Thr His Ile	Leu Val His Gly Asp	Asp Phe Ser Val Asn	Arg Gln	
	3190	3195	3200		
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	Ile Ser Val	Cys Gln Leu Asp Gly	Thr Trp Glu Pro Pro	Phe Ser	
	3220	3225	3230		
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45	Asp Glu Ser	Cys Ser Pro Val Ser	Cys Gly Lys Pro Glu	Ser Pro	
	3235	3240	3245		
	gaa cat gga	ttt gtg gtt ggc agt	aaa tac acc ttt gaa	agc aca	10786
	Glu His Gly	Phe Val Val Gly Ser	Lys Tyr Thr Phe Glu	Ser Thr	
	3250	3255	3260		

5	att att tat cag tgt gag cct ggc tat gaa ct <sup>a</sup> gag ggg aac agg Ile Ile Tyr Gln Cys Glu Pro Gly Tyr Glu Leu Glu Gly Asn Arg 3265 3270 3275	10831
	gaa cgt gtc tgc cag gag aac aga cag tgg agt gga ggg gtg gca Glu Arg Val Cys Gln Glu Asn Arg Gln Trp Ser Gly Gly Val Ala	10876
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	3295 3300 3305	10966
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20	cac tgc aca gaa aat gga acc tgg age cac cca gtc cct ctc tgc His Cys Thr Glu Asn Gly Thr Trp Ser His Pro Val Pro Leu Cys 3340 3345 3350	11101
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25	ctg ctg tct gaa aag gag ttt tat gtt gat cag aat gtg tcc atc Leu Leu Ser Glu Lys Glu Phe Tyr Val Asp Gln Asn Val Ser Ile 3370 3375 3380	11191
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30	tgc aac ccc gac gag acg tgg aca cag aca agc gcc aaa tgt gaa Cys Asn Pro Asp Glu Thr Trp Thr Gln Thr Ser Ala Lys Cys Glu 3400 3405 3410	11281
	3415 3420 3425	11326
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	3430 3435 3440	11416
40	tae agt gga tac atg ttg gag ggt ttc ctg agg agt gtt tgt tta Tyr Ser Gly Tyr Met Leu Glu Gly Phe Leu Arg Ser Val Cys Leu 3445 3450 3455	11461
	3460 3465 3470	11485
45	gaa aat gga aca tgg aca tca cct cct att tgc aga gct gtc tgt Glu Asn Gly Thr Trp Thr Ser Pro Pro Ile Cys Arg Ala Val Cys	
	3475 3480 3485	

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 Cys Ser Cys Pro Glu Gly Trp Met Gly Arg Leu Cys Glu Glu Pro  
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 Ile Cys Ile Leu Pro Cys Leu Asn Gly Gly Arg Cys Val Ala Pro  
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 20                 25                 30  
 Arg Leu Phe Pro Glu Thr Ala Pro Gly Ala Pro Gly Ser Ile Pro Ala  
 35                 40                 45  
 40   Pro Pro Ala Pro Gly Asp Glu Ala Ala Gly Ser Arg Val Glu Arg Leu  
 50                 55                 60  
 Gly Gln Ala Phe Arg Arg Arg Val Arg Leu Leu Arg Glu Leu Ser Glu  
 65                 70                 75                 80  
 Arg Leu Glu Leu Val Phe Leu Val Asp Asp Ser Ser Ser Val Gly Glu  
 45                 85                 90                 95  
 Val Asn Phe Arg Ser Glu Leu Met Phe Val Arg Lys Leu Leu Ser Asp  
 100                 105                 110  
 Phe Pro Val Val Pro Thr Ala Thr Arg Val Ala Ile Val Thr Phe Ser  
 115                 120                 125

5 Ser Lys Asn Tyr Val Val Pro Arg Val Asp Tyr Ile Ser Thr Arg Arg  
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 Ser Tyr Arg Gly Gly Thr Tyr Thr Lys Gly Ala Phe Gln Gln Ala  
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 Gln Gly Asn Ile Arg Glu Leu Asn Asp Met Ala Ser Thr Pro Lys Glu  
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 Glu Asn Gly Tyr Phe Ile Gln Asn Thr Cys Asn Asn His Phe Asn Ala  
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 40 405 410 415  
 Ile Ile Leu Cys Leu Pro Asn Gly Leu Trp Ser Gly Ser Glu Ser Tyr  
 420 425 430  
 Cys Arg Val Arg Thr Cys Pro His Leu Arg Gln Pro Lys His Gly His  
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 45 Ile Ser Cys Ser Thr Arg Glu Met Leu Tyr Lys Thr Thr Cys Leu Val  
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 Ala Cys Asp Glu Gly Tyr Arg Leu Glu Gly Ser Asp Lys Leu Thr Cys  
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 Asn Cys Gly Lys Gln Pro Ala Lys Phe Gly Thr Ile Cys Tyr Val Ser  
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 10 Cys Arg Gln Gly Phe Ile Leu Ser Gly Val Lys Glu Met Leu Arg Cys  
 530               535                   540  
 Thr Thr Ser Gly Lys Trp Asn Val Gly Val Gln Ala Ala Val Cys Lys  
 545               550                   555                   560  
 Asp Val Glu Ala Pro Gln Ile Asn Cys Pro Lys Asp Ile Glu Ala Lys  
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 Cys Leu Glu Gly Tyr Asp Phe Thr Glu Gly Ser Thr Asp Lys Tyr Tyr  
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 45               805                   810                   815  
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 820               825                   830  
 Phe Cys Ser Asp Ala Glu Asp Ile Asp Cys Arg Leu Glu Glu Asn Leu  
 835               840                   845

5. Thr Lys Lys Tyr Cys Leu Glu Tyr Asn Tyr Asp Tyr Glu Asn Gly Phe  
     850                  855                  860  
     Ala Ile Gly Pro Gly Gly Trp Gly Ala Ala Asn Arg Leu Asp Tyr Ser  
     865                  870                  875                  880  
     Tyr Asp Asp Phe Leu Asp Thr Val Gln Glu Thr Ala Thr Ser Ile Gly  
 10                  885                  890                  895  
     Asn Ala Lys Ser Ser Arg Ile Lys Arg Ser Ala Pro Leu Ser Asp Tyr  
     900                  905                  910  
     Lys Ile Lys Leu Ile Phe Asn Ile Thr Ala Ser Val Pro Leu Pro Asp  
     915                  920                  925  
 15. Glu Arg Asn Asp Thr Leu Glu Trp Glu Asn Gln Gln Arg Leu Leu Gln  
     930                  935                  940  
     Thr Leu Glu Thr Ile Thr Asn Lys Leu Lys Arg Thr Leu Asn Lys Asp  
     945                  950                  955                  960  
     Pro Met Tyr Ser Phe Gln Leu Ala Ser Glu Ile Leu Ile Ala Asp Ser  
 20                  965                  970                  975  
     Asn Ser Leu Glu Thr Lys Lys Ala Ser Pro Phe Cys Arg Pro Gly Ser  
     980                  985                  990  
     Val Leu Arg Gly Arg Met Cys Val Asn Cys Pro Leu Gly Thr Tyr Tyr  
     995                  1000                  1005  
 25. Asn Leu Glu His Phe Thr Cys Glu Ser Cys Arg Ile Gly Ser Tyr  
     1010                  1015                  1020  
     Gln Asp Glu Glu Gly Gln Leu Glu Cys Lys Leu Cys Pro Ser Gly  
     1025                  1030                  1035  
     Met Tyr Thr Glu Tyr Ile His Ser Arg Asn Ile Ser Asp Cys Lys  
 30                  1040                  1045                  1050  
     Ala Gln Cys Lys Gln Gly Thr Tyr Ser Tyr Ser Gly Leu Glu Thr  
     1055                  1060                  1065  
     Cys Glu Ser Cys Pro Leu Gly Thr Tyr Gln Pro Lys Phe Gly Ser  
     1070                  1075                  1080  
 35. Arg Ser Cys Leu Ser Cys Pro Glu Asn Thr Ser Thr Val Lys Arg  
     1085                  1090                  1095  
     Gly Ala Val Asn Ile Ser Ala Cys Gly Val Pro Cys Pro Glu Gly  
     1100                  1105                  1110  
     Lys Phe Ser Arg Ser Gly Leu Met Pro Cys His Pro Cys Pro Arg  
 40                  1115                  1120                  1125  
     Asp Tyr Tyr Gln Pro Asn Ala Gly Lys Ala Phe Cys Leu Ala Cys  
     1130                  1135                  1140  
     Pro Phe Tyr Gly Thr Thr Pro Phe Ala Gly Ser Arg Ser Ile Thr  
     1145                  1150                  1155  
 45. Glu Cys Ser Ser Phe Ser Ser Thr Phe Ser Ala Ala Glu Glu Ser  
     1160                  1165                  1170  
     Val Val Pro Pro Ala Ser Leu Gly His Ile Lys Lys Arg His Glu  
     1175                  1180                  1185  
     Ile Ser Ser Gln Val Phe His Glu Cys Phe Phe Asn Pro Cys His

5	1190	1195	1200
	Asn Ser Gly Thr Cys Gln Gln	Leu Gly Arg Gly Tyr Val Cys Leu	
	1205	1210	1215
	Cys Pro Leu Gly Tyr Thr Gly	Leu Lys Cys Glu Thr Asp Ile Asp	
	1220	1225	1230
10	Glu Cys Ser Pro Leu Pro Cys	Leu Asn Asn Gly Val Cys Lys Asp	
	1235	1240	1245
	Leu Val Gly Glu Phe Ile Cys	Glu Cys Pro Ser Gly Tyr Thr Gly	
	1250	1255	1260
	Gln Arg Cys Glu Glu Asn Ile	Asn Glu Cys Ser Ser Ser Pro Cys	
15	1265	1270	1275
	Leu Asn Lys Gly Ile Cys Val	Asp Gly Val Ala Gly Tyr Arg Cys	
	1280	1285	1290
	Thr Cys Val Lys Gly Phe Val	Gly Leu His Cys Glu Thr Glu Val	
	1295	1300	1305
20	Asn Glu Cys Gln Ser Asn Pro	Cys Leu Asn Asn Ala Val Cys Glu	
	1310	1315	1320
	Asp Gln Val Gly Gly Phe Leu	Cys Lys Cys Pro Pro Gly Phe Leu	
	1325	1330	1335
	Gly Thr Arg Cys Gly Lys Asn	Val Asp Glu Cys Leu Ser Gln Pro	
25	1340	1345	1350
	Cys Lys Asn Gly Ala Thr Cys	Lys Asp Gly Ala Asn Ser Phe Arg	
	1355	1360	1365
	Cys Leu Cys Ala Ala Gly Phe	Thr Gly Ser His Cys Glu Leu Asn	
	1370	1375	1380
30	Ile Asn Glu Cys Gln Ser Asn	Pro Cys Arg Asn Gln Ala Thr Cys	
	1385	1390	1395
	Val Asp Glu Leu Asn Ser Tyr	Ser Cys Lys Cys Gln Pro Gly Phe	
	1400	1405	1410
	Ser Gly Lys Arg Cys Glu Thr	Glu Gln Ser Thr Gly Phe Asn Leu	
35	1415	1420	1425
	Asp Phe Glu Val Ser Gly Ile	Tyr Gly Tyr Val Met Leu Asp Gly	
	1430	1435	1440
	Met Leu Pro Ser Leu His Ala	Leu Thr Cys Thr Phe Trp Met Lys	
	1445	1450	1455
40	Ser Ser Asp Asp Met Asn Tyr	Gly Thr Pro Ile Ser Tyr Ala Val	
	1460	1465	1470
	Asp Asn Gly Ser Asp Asn Thr	Leu Leu Leu Thr Asp Tyr Asn Gly	
	1475	1480	1485
	Trp Val Leu Tyr Val Asn Gly	Arg Glu Lys Ile Thr Asn Cys Pro	
45	1490	1495	1500
	Ser Val Asn Asp Gly Arg Trp	His His Ile Ala Ile Thr Trp Thr	
	1505	1510	1515
	Ser Ala Asn Gly Ile Trp Lys	Val Tyr Ile Asp Gly Lys Leu Ser	
	1520	1525	1530

5 Asp Gly Gly Ala Gly Leu Ser Val Gly Leu Pro Ile Pro Gly Gly  
 1535- 1540 1545  
 Gly Ala Leu Val Leu Gly Gln Glu Gln Asp Lys Lys Gly Glu Gly  
 1550 1555 1560  
 Phe Ser Pro Ala Glu Ser Phe Val Gly Ser Ile Ser Gln Leu Asn  
 10 1565 1570 1575  
 Leu Trp Asp Tyr Val Leu Ser Pro Gln Gln Val Lys Ser Leu Ala  
 1580 1585 1590  
 Thr Ser Cys Pro Glu Glu Leu Ser Lys Gly Asn Val Leu Ala Trp  
 1595 1600 1605  
 15 Pro Asp Phe Leu Ser Gly Ile Val Gly Lys Val Lys Ile Asp Ser  
 1610 1615 1620  
 Lys Ser Ile Phe Cys Ser Asp Cys Pro Arg Leu Gly Gly Ser Val  
 1625 1630 1635  
 Pro His Leu Arg Thr Ala Ser Glu Asp Leu Lys Pro Gly Ser Lys  
 20 1640 1645 1650  
 Val Asn Leu Phe Cys Asp Pro Gly Phe Gln Leu Val Gly Asn Pro  
 1655 1660 1665  
 Val Gln Tyr Cys Leu Asn Gln Gly Gln Trp Thr Gln Pro Leu Pro  
 1670 1675 1680  
 25 His Cys Glu Arg Ile Ser Cys Gly Val Pro Pro Pro Leu Glu Asn  
 1685 1690 1695  
 Gly Phe His Ser Ala Asp Asp Phe Tyr Ala Gly Ser Thr Val Thr  
 1700 1705 1710  
 Tyr Gln Cys Asn Asn Gly Tyr Tyr Leu Leu Gly Asp Ser Arg Met  
 30 1715 1720 1725  
 Phe Cys Thr Asp Asn Gly Ser Trp Asn Gly Val Ser Pro Ser Cys  
 1730 1735 1740  
 Leu Asp Val Asp Glu Cys Ala Val Gly Ser Asp Cys Ser Glu His  
 1745 1750 1755  
 35 Ala Ser Cys Leu Asn Val Asp Gly Ser Tyr Ile Cys Ser Cys Val  
 1760 1765 1770  
 Pro Pro Tyr Thr Gly Asp Gly Lys Asn Cys Ala Glu Pro Ile Lys  
 1775 1780 1785  
 Cys Lys Ala Pro Gly Asn Pro Glu Asn Gly His Ser Ser Gly Glu  
 40 1790 1795 1800  
 Ile Tyr Thr Val Gly Ala Ala Val Thr Phe Ser Cys Gln Glu Gly  
 1805 1810 1815  
 Tyr Gln Leu Met Gly Val Thr Lys Ile Thr Cys Leu Glu Ser Gly  
 1820 1825 1830  
 45 Glu Trp Asn His Leu Ile Pro Tyr Cys Lys Ala Val Ser Cys Gly  
 1835 1840 1845  
 Lys Pro Ala Ile Pro Glu Asn Gly Cys Ile Glu Glu Leu Ala Phe  
 1850 1855 1860  
 Thr Phe Gly Ser Lys Val Thr Tyr Arg Cys Asn Lys Gly Tyr Thr

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5	1865	1870	1875
	Leu Ala Gly Asp Lys Glu Ser Ser Cys Leu Ala Asn Ser Ser Trp		
	1880	1885	1890
	Ser His Ser Pro Pro Val Cys Glu Pro Val Lys Cys Ser Ser Pro		
	1895	1900	1905
10	Glu Asn Ile Asn Asn Gly Lys Tyr Ile Leu Ser Gly Leu Thr Tyr		
	1910	1915	1920
	Leu Ser Thr Ala Ser Tyr Ser Cys Asp Thr Gly Tyr Ser Leu Gln		
	1925	1930	1935
	Gly Pro Ser Ile Ile Glu Cys Thr Ala Ser Gly Ile Trp Asp Arg		
15	1940	1945	1950
	Ala Pro Pro Ala Cys His Leu Val Phe Cys Gly Glu Pro Pro Ala		
	1955	1960	1965
	Ile Lys Asp Ala Val Ile Thr Gly Asn Asn Phe Thr Phe Arg Asn		
	1970	1975	1980
20	Thr Val Thr Tyr Thr Cys Lys Glu Gly Tyr Thr Leu Ala Gly Leu		
	1985	1990	1995
	Asp Thr Ile Glu Cys Leu Ala Asp Gly Lys Trp Ser Arg Ser Asp		
	2000	2005	2010
	Gln Gln Cys Leu Ala Val Ser Cys Asp Glu Pro Pro Ile Val Asp		
25	2015	2020	2025
	His Ala Ser Pro Glu Thr Ala His Arg Leu Phe Gly Asp Ile Ala		
	2030	2035	2040
	Phe Tyr Tyr Cys Ser Asp Gly Tyr Ser Leu Ala Asp Asn Ser Gln		
	2045	2050	2055
30	Leu Leu Cys Asn Ala Gln Gly Lys Trp Val Pro Pro Glu Gly Gln		
	2060	2065	2070
	Asp Met Pro Arg Cys Ile Ala His Phe Cys Glu Lys Pro Pro Ser		
	2075	2080	2085
	Val Ser Tyr Ser Ile Leu Glu Ser Val Ser Lys Ala Lys Phe Ala		
35	2090	2095	2100
	Ala Gly Ser Val Val Ser Phe Lys Cys Met Glu Gly Phe Val Leu		
	2105	2110	2115
	Asn Thr Ser Ala Lys Ile Glu Cys Met Arg Gly Gly Gln Trp Asn		
	2120	2125	2130
40	Pro Ser Pro Met Ser Ile Gln Cys Ile Pro Val Arg Cys Gly Glu		
	2135	2140	2145
	Pro Pro Ser Ile Met Asn Gly Tyr Ala Ser Gly Ser Asn Tyr Ser		
	2150	2155	2160
	Phe Gly Ala Met Val Ala Tyr Ser Cys Asn Lys Gly Phe Tyr Ile		
45	2165	2170	2175
	Lys Gly Glu Lys Lys Ser Thr Cys Glu Ala Thr Gly Gln Trp Ser		
	2180	2185	2190
	Ser Pro Ile Pro Thr Cys His Pro Val Ser Cys Gly Glu Pro Pro		
	2195	2200	2205

5 Lys Val Glu Asn Gly Phe Leu Glu His Thr Thr Gly Arg Ile Phe  
 2210 2215 2220  
 Glu Ser Glu Val Arg Tyr Gln Cys Asn Pro Gly Tyr Lys Ser Val  
 2225 2230 2235  
 Gly Ser Pro Val Phe Val Cys Gln Ala Asn Arg His Trp His Ser  
 10 2240 2245 2250  
 Glu Ser Pro Leu Met Cys Val Pro Leu Asp Cys Gly Lys Pro Pro  
 2255 2260 2265  
 Pro Ile Gln Asn Gly Phe Met Lys Gly Glu Asn Phe Glu Val Gly  
 2270 2275 2280  
 15 Ser Lys Val Gln Phe Phe Cys Asn Glu Gly Tyr Glu Leu Val Gly  
 2285 2290 2295  
 Asp Ser Ser Trp Thr Cys Gln Lys Ser Gly Lys Trp Asn Lys Lys  
 2300 2305 2310  
 Ser Asn Pro Lys Cys Met Pro Ala Lys Cys Pro Glu Pro Pro Leu  
 20 2315 2320 2325  
 Leu Glu Asn Gln Leu Val Leu Lys Glu Leu Thr Thr Glu Val Gly  
 2330 2335 2340  
 Val Val Thr Phe Ser Cys Lys Glu Gly His Val Leu Gln Gly Pro  
 2345 2350 2355  
 25 Ser Val Leu Lys Cys Leu Pro Ser Gln Gln Trp Asn Asp Ser Phe  
 2360 2365 2370  
 Pro Val Cys Lys Ile Val Leu Cys Thr Pro Pro Pro Leu Ile Ser  
 2375 2380 2385  
 Phe Gly Val Pro Ile Pro Ser Ser Ala Leu His Phe Gly Ser Thr  
 30 2390 2395 2400  
 Val Lys Tyr Ser Cys Val Gly Gly Phe Phe Leu Arg Gly Asn Ser  
 2405 2410 2415  
 Thr Thr Leu Cys Gln Pro Asp Gly Thr Trp Ser Ser Pro Leu Pro  
 2420 2425 2430  
 35 Glu Cys Val Pro Val Glu Cys Pro Gln Pro Glu Glu Ile Pro Asn  
 2435 2440 2445  
 Gly Ile Ile Asp Val Gln Gly Leu Ala Tyr Leu Ser Thr Ala Leu  
 2450 2455 2460  
 Tyr Thr Cys Lys Pro Gly Phe Glu Leu Val Gly Asn Thr Thr Thr  
 40 2465 2470 2475  
 Leu Cys Gly Glu Asn Gly His Trp Leu Gly Gly Lys Pro Thr Cys  
 2480 2485 2490  
 Lys Ala Ile Glu Cys Leu Lys Pro Lys Glu Ile Leu Asn Gly Lys  
 2495 2500 2505  
 45 Phe Ser Tyr Thr Asp Leu His Tyr Gly Gln Thr Val Thr Tyr Ser  
 2510 2515 2520  
 Cys Asn Arg Gly Phe Arg Leu Glu Gly Pro Ser Ala Leu Thr Cys  
 2525 2530 2535  
 Leu Glu Thr Gly Asp Trp Asp Val Asp Ala Pro Ser Cys Asn Ala

5	2540	2545	2550
	Ile His Cys Asp Ser Pro Gln Pro Ile Glu Asn Gly Phe Val Glu		
	2555	2560	2565
	Gly Ala Asp Tyr Ser Tyr Gly Ala Ile Ile Ile Tyr Ser Cys Phe		
	2570	2575	2580
10	Pro Gly Phe Gln Val Ala Gly His Ala Met Gln Thr Cys Glu Glu		
	2585	2590	2595
	Ser Gly Trp Ser Ser Ser Ile Pro Thr Cys Met Pro Ile Asp Cys		
	2600	2605	2610
	Gly Leu Pro Pro His Ile Asp Phe Gly Asp Cys Thr Lys Leu Lys		
15	2615	2620	2625
	Asp Asp Gln Gly Tyr Phe Glu Gln Glu Asp Asp Met Met Glu Val		
	2630	2635	2640
	Pro Tyr Val Thr Pro His Pro Pro Tyr His Leu Gly Ala Val Ala		
	2645	2650	2655
20	Lys Thr Trp Glu Asn Thr Lys Glu Ser Pro Ala Thr His Ser Ser		
	2660	2665	2670
	Asn Phe Leu Tyr Gly Thr Met Val Ser Tyr Thr Cys Asn Pro Gly		
	2675	2680	2685
	Tyr Glu Leu Leu Gly Asn Pro Val Leu Ile Cys Gln Glu Asp Gly		
25	2690	2695	2700
	Thr Trp Asn Gly Ser Ala Pro Ser Cys Ile Ser Ile Glu Cys Asp		
	2705	2710	2715
	Leu Pro Thr Ala Pro Glu Asn Gly Phe Leu Arg Phe Thr Glu Thr		
	2720	2725	2730
30	Ser Met Gly Ser Ala Val Gln Tyr Ser Cys Lys Pro Gly His Ile		
	2735	2740	2745
	Leu Ala Gly Ser Asp Leu Arg Leu Cys Leu Glu Asn Arg Lys Trp		
	2750	2755	2760
	Ser Gly Ala Ser Pro Arg Cys Glu Ala Ile Ser Cys Lys Lys Pro		
35	2765	2770	2775
	Asn Pro Val Met Asn Gly Ser Ile Lys Gly Ser Asn Tyr Thr Tyr		
	2780	2785	2790
	Leu Ser Thr Leu Tyr Tyr Glu Cys Asp Pro Gly Tyr Val Leu Asn		
	2795	2800	2805
40	Gly Thr Glu Arg Arg Thr Cys Gln Asp Asp Lys Asn Trp Asp Glu		
	2810	2815	2820
	Asp Glu Pro Ile Cys Ile Pro Val Asp Cys Ser Ser Pro Pro Val		
	2825	2830	2835
	Ser Ala Asn Gly Gln Val Arg Gly Asp Glu Tyr Thr Phe Gln Lys		
45	2840	2845	2850
	Glu Ile Glu Tyr Thr Cys Asn Glu Gly Phe Leu Leu Glu Gly Ala		
	2855	2860	2865
	Arg Ser Arg Val Cys Leu Ala Asn Gly Ser Trp Ser Gly Ala Thr		
	2870	2875	2880

5 Pro Asp Cys Val Pro Val Arg Cys Ala Thr Pro Pro Gln Leu Ala  
 2885 2890 2895  
 Asn Gly Val Thr Glu Gly Leu Asp Tyr Gly Phe Met Lys Glu Val  
 2900 2905 2910  
 Thr Phe His Cys His Glu Gly Tyr Ile Leu His Gly Ala Pro Lys  
 10 2915 2920 2925  
 Leu Thr Cys Gln Ser Asp Gly Asn Trp Asp Ala Glu Ile Pro Leu  
 2930 2935 2940  
 Cys Lys Pro Val Asn Cys Gly Pro Pro Glu Asp Leu Ala His Gly  
 2945 2950 2955  
 15 Phe Pro Asn Gly Phe Ser Phe Ile His Gly Gly His Ile Gln Tyr  
 2960 2965 2970  
 Gln Cys Phe Pro Gly Tyr Lys Leu His Gly Asn Ser Ser Arg Arg  
 2975 2980 2985  
 Cys Leu Ser Asn Gly Ser Trp Ser Gly Ser Ser Pro Ser Cys Leu  
 20 2990 2995 3000  
 Pro Cys Arg Cys Ser Thr Pro Val Ile Glu Tyr Gly Thr Val Asn  
 3005 3010 3015  
 Gly Thr Asp Phe Asp Cys Gly Lys Ala Ala Arg Ile Gln Cys Phe  
 3020 3025 3030  
 25 Lys Gly Phe Lys Leu Leu Gly Leu Ser Glu Ile Thr Cys Glu Ala  
 3035 3040 3045  
 Asp Gly Gln Trp Ser Ser Gly Phe Pro His Cys Glu His Thr Ser  
 3050 3055 3060  
 Cys Gly Ser Leu Pro Met Ile Pro Asn Ala Phe Ile Ser Glu Thr  
 30 3065 3070 3075  
 Ser Ser Trp Lys Glu Asn Val Ile Thr Tyr Ser Cys Arg Ser Gly  
 3080 3085 3090  
 Tyr Val Ile Gln Gly Ser Ser Asp Leu Ile Cys Thr Glu Lys Gly  
 3095 3100 3105  
 35 Val Trp Ser Gln Pro Tyr Pro Val Cys Glu Pro Leu Ser Cys Gly  
 3110 3115 3120  
 Ser Pro Pro Ser Val Ala Asn Ala Val Ala Thr Gly Glu Ala His  
 3125 3130 3135  
 Thr Tyr Glu Ser Glu Val Lys Leu Arg Cys Leu Glu Gly Tyr Thr  
 40 3140 3145 3150  
 Met Asp Thr Asp Thr Asp Thr Phe Thr Cys Gln Lys Asp Gly Arg  
 3155 3160 3165  
 Trp Phe Pro Glu Arg Ile Ser Cys Ser Pro Lys Lys Cys Pro Leu  
 3170 3175 3180  
 45 Pro Glu Asn Ile Thr His Ile Leu Val His Gly Asp Asp Phe Ser  
 3185 3190 3195  
 Val Asn Arg Gln Val Ser Val Ser Cys Ala Glu Gly Tyr Thr Phe  
 3200 3205 3210  
 Glu Gly Val Arg Ile Ser Val Cys Gln Leu Asp Gly Thr Trp Glu

5	3215	3220	3225
	Pro Pro Phe Ser Asp Glu Ser	Cys Ser Pro Val Ser	Cys Gly Lys
	3230	3235	3240
	Pro Glu Ser Pro Glu His Gly	Phe Val Val Gly Ser	Lys Tyr Thr
	3245	3250	3255
10	Phe Glu Ser Thr Ile Ile Tyr	Gln Cys Glu Pro Gly	Tyr Glu Leu
	3260	3265	3270
	Glu Gly Asn Arg Glu Arg Val	Cys Gln Glu Asn Arg	Gln Trp Ser
	3275	3280	3285
	Gly Gly Val Ala Ile Cys Lys	Glu Thr Arg Cys Glu	Thr Pro Leu
15	3290	3295	3300
	Glu Phe Leu Asn Gly Lys Ala	Asp Ile Glu Asn Arg	Thr Thr Gly
	3305	3310	3315
	Pro Asn Val Val Tyr Ser Cys	Asn Arg Gly Tyr Ser	Leu Glu Gly
	3320	3325	3330
20	Pro Ser Glu Ala His Cys Thr	Glu Asn Gly Thr Trp	Ser His Pro
	3335	3340	3345
	Val Pro Leu Cys Lys Pro Asn	Pro Cys Pro Val Pro	Phe Val Ile
	3350	3355	3360
	Pro Glu Asn Ala Leu Leu Ser	Glu Lys Glu Phe Tyr	Val Asp Gln
25	3365	3370	3375
	Asn Val Ser Ile Lys Cys Arg	Glu Gly Phe Leu Leu	Gln Gly His
	3380	3385	3390
	Gly Ile Ile Thr Cys Asn Pro	Asp Glu Thr Trp Thr	Gln Thr Ser
	3395	3400	3405
30	Ala Lys Cys Glu Lys Ile Ser	Cys Gly Pro Pro Ala	His Val Glu
	3410	3415	3420
	Asn Ala Ile Ala Arg Gly Val	His Tyr Gln Tyr Gly	Asp Met Ile
	3425	3430	3435
	Thr Tyr Ser Cys Tyr Ser Gly	Tyr Met Leu Glu Gly	Phe Leu Arg
35	3440	3445	3450
	Ser Val Cys Leu Glu Asn Gly	Thr Trp Thr Ser Pro	Pro Ile Cys
	3455	3460	3465
	Arg Ala Val Cys Arg Phe Pro	Cys Gln Asn Gly	Ile Cys Gln
	3470	3475	3480
40	Arg Pro Asn Ala Cys Ser Cys	Pro Glu Gly Trp Met	Gly Arg Leu
	3485	3490	3495
	Cys Glu Glu Pro Ile Cys Ile	Leu Pro Cys Leu Asn	Gly Gly Arg
	3500	3505	3510
	Cys Val Ala Pro Tyr Gln Cys	Asp Cys Pro Pro Gly	Trp Thr Gly
45	3515	3520	3525
	Ser Arg Cys His Thr Ala Val	Cys Gln Ser Pro Cys	Leu Asn Gly
	3530	3535	3540
	Gly Lys Cys Val Arg Pro Asn	Arg Cys His Cys Leu	Ser Ser Trp
	3545	3550	3555

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5 Thr Gly His Asn Cys Ser Arg Lys Arg Arg Thr Gly Phe  
3560 - 3565 3570